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Sir:

Transmitted herewith for filing is the continuation-in-part patent application of

Inventor(s): Kenneth Rhodes and Wenqian An

For: METHODS FOR TREATING CARDIOVASCULAR DISORDERS

Enclosed are:

☒ This is a request for filing a ☒ continuation-in-part ☐ divisional application under 37 CFR 1.53(b), of pending prior application serial no. 09/350,874, filed on July 9, 1999 entitled METHODS FOR TREATING CARDIOVASCULAR DISORDERS.

☒ 62 pages of specification, 2 pages of claims, 1 page of abstract.

☒ 46 sheets of informal drawings (Figures 1-41).

☒ An unexecuted Declaration, Petition and Power of Attorney.

☒ 92 pages of sequence listing.

☐ An assignment of the invention to _____. A recordation form cover sheet (Form PTO 1595) is also enclosed.

☐ A verified statement to establish small entity status under 37 C.F.R. 1.9 and 37 C.F.R. 1.27.

☒ Other Transmittal Letter for Diskette of Sequence Listing; and Diskette of Sequence Listing

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METHODS FOR TREATING CARDIOVASCULAR DISORDERS

Related Applications

This application claims priority to U.S. provisional Application No. 60/110,033, filed on November 25, 1998, U.S. provisional Application No. 60/109,333, filed on November 20, 1998, U.S. provisional Application No. 60/110,277, filed on November 30, 1998, U.S. Patent Application No.: 09/298,731, filed on April 23, 1999, U.S. Patent Application No.: 09/350,614, filed on July 9, 1999, and U.S. Patent Application No.: 09/350,874, filed on July 9, 1999, incorporated herein in their entirety by this reference.

Background of the Invention

Mammalian cell membranes are important to the structural integrity and activity of many cells and tissues. Of particular interest in membrane physiology is the study of trans-membrane ion channels which act to directly control a variety of pharmacological, physiological, and cellular processes. Numerous ion channels have been identified including calcium, sodium, and potassium channels, each of which have been investigated to determine their roles in vertebrate and insect cells.

Because of their involvement in maintaining normal cellular homeostasis, much attention has been given to potassium channels. A number of these potassium channels open in response to changes in the cell membrane potential. Many voltage-gated potassium channels have been identified and characterized by their electrophysiological and pharmacological properties. Potassium currents are more diverse than sodium or calcium currents and are further involved in determining the response of a cell to external stimuli.

The diversity of potassium channels and their important physiological role highlights their potential as targets for developing therapeutic agents for various diseases. One of the best characterized classes of potassium channels are the voltage-gated potassium channels. The prototypical member of this class is the protein encoded by the Shaker gene in *Drosophila melanogaster*. Proteins of the Shal or Kv4 family are a type of voltage-gated potassium channels that underlies many of the native A type currents that have been recorded from different primary cells. Kv4 channels have a major role in the repolarization of cardiac action potentials. In neurons, Kv4 channels and the A currents they may comprise play an important role in modulation of firing rate, action potential initiation and in controlling dendritic responses to synaptic inputs.

The Kv family of channels includes, among others: (1) the delayed-rectifier potassium channels, which repolarize the membrane after each action potential to prepare the cell to fire again; and (2) the rapidly inactivating (A-type) potassium channels, which are

active predominantly at subthreshold voltages and and act to reduce the rate at which excitable cells reach firing threshold. In addition to being critical for action potential conduction, Kv channels also control the response to depolarizing, e.g., synaptic, inputs and play a role in neurotransmitter release. As a result of these activities, voltage-gated potassium channels are key regulators of neuronal excitability (Hille B., Ionic Channels of Excitable Membranes, Second Edition, Sunderland, MA: Sinauer, (1992)).

There is tremendous structural and functional diversity within the Kv potassium channel superfamily. This diversity is generated both by the existence of multiple genes and by alternative splicing of RNA transcripts produced from the same gene. Nonetheless, the amino acid sequences of the known Kv potassium channels show high similarity. All appear to be comprised of four, pore forming α-subunits and some are known to have four cytoplasmic (β-subunit) polypeptides (Jan L.Y. et al. (1990) *Trends Neurosci* 13:415-419, and Pongs, O. et al. (1995) *Sem Neurosci.* 7:137-146). The known Kv channel α-subunits fall into four sub-families named for their homology to channels first isolated from *Drosophila*: the Kv1, or *Shaker*-related subfamily; the Kv2, or *Shab*-related subfamily; the Kv3, or *Shaw*-related subfamily; and the Kv4, or *Shal*-related subfamily.

Kv4.2 and Kv4.3 are examples of Kv channel α-subunits of the *Shal*-related subfamily. Kv4.3 has a unique neuroanatomical distribution in that its mRNA is highly expressed in brainstem monoaminergic and forebrain cholinergic neurons, where it is involved in the release of the neurotransmitters dopamine, norepinephrine, serotonin, and acetylcholine. This channel is also highly expressed in cortical pyramidal cells and in interneurons. (Serdio P. et al. (1996) *J. Neurophys* 75:2174-2179). Interestingly, the Kv4.3 polypeptide is highly expressed in neurons which express the corresponding mRNA. The Kv4.3 polypeptide is expressed in the somatodendritic membranes of these cells, where it is thought to contribute to the rapidly inactivating K+ conductance. Kv4.2 mRNA is widely expressed in brain, and the corresponding polypeptide also appears to be concentrated in somatodendritic membranes where it also contributes to the rapidly inactivating K^+ conductance (Sheng et al. (1992) Neuron 9:271-84). These somatodendritic A-type Kv channels, like Kv4.2 and Kv4.3 are likely involved in processes which underlie learning and memory, such as integration of sub-threshold synaptic responses and the conductance of back-propagating action potentials (Hoffman D.A. et al. (1997) *Nature* 387:869-875).

Thus, proteins which interact with and modulate the activity of potassium channel proteins e.g., potassium channels having a Kv4.2 or Kv4.3 subunit, provide novel molecular targets to modulate neuronal excitability, e.g., action potential conduction, somatodendritic excitability and neurotransmitter release, in cells expressing these channels. In addition, detection of genetic lesions in the gene encoding these proteins could be used to diagnose and treat cardiovascular disorders such as heart failure, hypertension, atrial fibrillation, dilated cardiomyopathy, idiopathic cardiomyopathy, or angina.

Summary of the Invention

The present invention is based, at least in part, on the discovery of novel nucleic acid molecules which encode gene products that interact with potassium channel proteins or possess substantial homology to the gene products of the invention that interact with potassium channel proteins (paralogs). Potassium channel proteins are, for example, potassium channels having a Kv4.2 or Kv4.3 subunit. The nucleic acid molecules of the invention and their gene products are referred to herein as "Potassium Channel Interacting Proteins", "PCIP", or "KChIP" nucleic acid and protein molecules. The PCIP molecules of the present invention are useful as modulating agents to regulate a variety of cellular processes, in particular, cardiac cell processes.

Accordingly, in one aspect, this invention provides a method for identifying a compound suitable for treating a cardiovascular disorder, e.g., arteriosclerosis, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrilation or congestive heart failure, by contacting a PCIP polypeptide or a fragment thereof, or a cell expressing a PCIP polypeptide or a fragment thereof with a test compound and determining whether the PCIP polypeptide or fragment thereof binds to the test compound, thereby identifying a compound suitable for treating a cardiovascular disorder. In a preferred embodiment, the binding of the test compound to the PCIP polypeptide or fragment thereof is detected by direct detection of test compound/polypeptide binding. In another embodiment, the binding of the test compound to the PCIP polypeptide or fragment thereof is detected by using a competition binding assay. In yet another embodiment, the

binding of the test compound to the PCIP polypeptide or fragment thereof is detected by using an assay for PCIP activity.

In another aspect, the invention features a method for identifying a compound suitable for treating a cardiovascular disorder, e.g., arteriosclerosis, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrilation or congestive heart failure, by incubating a cell expressing a potassium channel comprising a Kv4.3 or Kv4.2 subunit, or a fragment of a potassium channel comprising a Kv4.3 or Kv4.2 subunit, and a PCIP polypeptide or fragment thereof, in the presence and absence of a candidate compound; and determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with the PCIP polypeptide or fragment thereof, thereby identifying a compound suitable for treating a cardiovascular disorder.

In yet another aspect, the invention features a method for treating a cardiovascular disorder by contacting a potassium channel with an effective amount of a compound that modulates the binding of a PCIP protein to the potassium channel.

In a further aspect, the invention features a method for determining if a subject is at risk for a cardiovascular disorder by detecting, in a sample of cells from the subject an alteration in a PCIP gene which causes a mutated PCIP polypeptide to be produced, an alteration in a PCIP gene which causes abnormal expression of a PCIP polypeptide, or an alteration in a PCIP gene which causes abnormal processing of a PCIP polypeptide.

In another aspect, the invention features a method for identifying a subject suffering from a cardiovascular disorder by detecting, in a sample of cells from the subject an alteration in a PCIP gene which causes a mutated PCIP polypeptide to be produced, an alteration in a PCIP gene which causes abnormal expression of a PCIP polypeptide, or an alteration in a PCIP gene which causes abnormal processing of a PCIP polypeptide.

In a preferred embodiment, the cardiovascular disorder is associated with an abnormal I_{to} current.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

Brief Description of the Drawings

Figure 1 depicts the cDNA sequence and predicted amino acid sequence of human 1v. The nucleotide sequence corresponds to nucleic acids 1 to 1463 of SEQ ID NO:1. The amino acid sequence corresponds to amino acids 1 to 216 of SEQ ID NO:2.

Figure 2 depicts the cDNA sequence and predicted amino acid sequence of rat 1v. The nucleotide sequence corresponds to nucleic acids 1 to 1856 of SEQ ID NO:3. The amino acid sequence corresponds to amino acids 1 to 245 of SEQ ID NO:4.

Figure 3 depicts the cDNA sequence and predicted amino acid sequence of mouse 1v. The nucleotide sequence corresponds to nucleic acids 1 to 1907 of SEQ ID NO:5. The amino acid sequence corresponds to amino acids 1 to 216 of SEQ ID NO:6.

Figure 4 depicts the cDNA sequence and predicted amino acid sequence of rat 1vl. The nucleotide sequence corresponds to nucleic acids 1 to 1534 of SEQ ID NO:7. The amino acid sequence corresponds to amino acids 1 to 227 of SEQ ID NO:8.

Figure 5 depicts the cDNA sequence and predicted amino acid sequence of mouse 1vl. The nucleotide sequence corresponds to nucleic acids 1 to 1540 of SEQ ID NO:9. The amino acid sequence corresponds to amino acids 1 to 227 of SEQ ID NO:10.

Figure 6 depicts the cDNA sequence and predicted amino acid sequence of rat 1vn. The nucleotide sequence corresponds to nucleic acids 1 to 955 of SEQ ID NO:11. The amino acid sequence corresponds to amino acids 1 to 203 of SEQ ID NO:12.

Figure 7 depicts the cDNA sequence and predicted amino acid sequence of human 9ql. The nucleotide sequence corresponds to nucleic acids 1 to 2009 of SEQ ID NO:13. The amino acid sequence corresponds to amino acids 1 to 270 of SEQ ID NO:14.

Figure 8 depicts the cDNA sequence and predicted amino acid sequence of rat 9ql. The nucleotide sequence corresponds to nucleic acids 1 to 1247 of SEQ ID NO:15. The amino acid sequence corresponds to amino acids 1 to 257 of SEQ ID NO:16.

Figure 9 depicts the cDNA sequence and predicted amino acid sequence of mouse 9ql. The nucleotide sequence corresponds to nucleic acids 1 to 2343 of SEQ ID NO:17. The amino acid sequence corresponds to amino acids 1 to 270 of SEQ ID NO:18.

Figure 10 depicts the cDNA sequence and predicted amino acid sequence of human 9qm. The nucleotide sequence corresponds to nucleic acids 1 to 1955 of SEQ ID NO:19. The amino acid sequence corresponds to amino acids 1 to 252 of SEQ ID NO:20.

Figure 11 depicts the cDNA sequence and predicted amino acid sequence of rat 9qm. The nucleotide sequence corresponds to nucleic acids 1 to 2300 of SEQ ID NO:21. The amino acid sequence corresponds to amino acids 1 to 252 of SEQ ID NO:22.

Figure 12 depicts the cDNA sequence and predicted amino acid sequence of human 9qs. The nucleotide sequence corresponds to nucleic acids 1 to 1859 of SEQ ID NO:23. The amino acid sequence corresponds to amino acids 1 to 220 of SEQ ID NO:24.

Figure 13 depicts the cDNA sequence and predicted amino acid sequence of monkey 9qs. The nucleotide sequence corresponds to nucleic acids 1 to 2191 of SEQ ID NO:25. The amino acid sequence corresponds to amino acids 1 to 220 of SEQ ID NO:26.

Figure 14 depicts the cDNA sequence and predicted amino acid sequence of rat 9qc. The nucleotide sequence corresponds to nucleic acids 1 to 2057 of SEQ ID NO:27. The amino acid sequence corresponds to amino acids 1 to 252 of SEQ ID NO:28.

Figure 15 depicts the cDNA sequence and predicted amino acid sequence of rat 8t. The nucleotide sequence corresponds to nucleic acids 1 to 1904 of SEQ ID NO:29. The amino acid sequence corresponds to amino acids 1 to 225 of SEQ ID NO:30.

Figure 16 depicts the cDNA sequence and predicted amino acid sequence of human p19. The nucleotide sequence corresponds to nucleic acids 1 to 619 of SEQ ID NO:31. The amino acid sequence corresponds to amino acids 1 to 200 of SEQ ID NO:32.

Figure 17 depicts the cDNA sequence and predicted amino acid sequence of rat p19 The nucleotide sequence corresponds to nucleic acids 1 to 442 of SEQ ID NO:33. The amino acid sequence corresponds to amino acids 1 to 109 of SEQ ID NO:34.

Figure 18 depicts the cDNA sequence and predicted amino acid sequence of mouse p19. The nucleotide sequence corresponds to nucleic acids 1 to 2644 of SEQ ID NO:35. The amino acid sequence corresponds to amino acids 1 to 256 of SEQ ID NO:36.

Figure 19 depicts the cDNA sequence and predicted amino acid sequence of human W28559. The nucleotide sequence corresponds to nucleic acids 1 to 380 of SEQ ID NO:37. The amino acid sequence corresponds to amino acids 1 to 126 of SEQ ID NO:38.

Figure 20 depicts the cDNA sequence and predicted amino acid sequence of human P193. The nucleotide sequence corresponds to nucleic acids 1 to 2176 of SEQ ID NO:39. The amino acid sequence corresponds to amino acids 1 to 41 of SEQ ID NO:40.

Figure 21 depicts a schematic representation of the rat 1v, the rat 9qm, and the mouse P19 proteins, aligned to indicate the conserved domains among these proteins.

Figure 22 depicts the genomic DNA sequence of human 9q. *Figure 22A* depicts exon 1 and its flanking intron sequences (SEQ ID NO:46). *Figure 22B* depicts exons 2-11 and the flanking intron sequences (SEQ ID NO:47).

Figure 23 depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4a. The nucleotide sequence corresponds to nucleic acids 1 to 2413 of SEQ ID NO:48. The amino acid sequence corresponds to amino acids 1 to 233 of SEQ ID NO:49.

Figure 24 depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4b. The nucleotide sequence corresponds to nucleic acids 1 to 1591 of SEQ ID NO:50. The amino acid sequence corresponds to amino acids 1 to 233 of SEQ ID NO:51.

Figure 25 depicts an alignment of KChIP4a, KchIP4b, 9ql, 1v, p19, and related human paralog (hsncspara) W28559. Amino acids identical to the consensus are shaded in black, conserved amino acids are shaded in gray.

Figure 26 depicts the cDNA sequence and predicted amino acid sequence of rat 33b07. The nucleotide sequence corresponds to nucleic acids 1 to 2051 of SEQ ID NO:52. The amino acid sequence corresponds to amino acids 1 to 407 of SEQ ID NO:53.

Figure 27 depicts the cDNA sequence and predicted amino acid sequence of human 33b07. The nucleotide sequence corresponds to nucleic acids 1 to 4148 of SEQ ID NO:54. The amino acid sequence corresponds to amino acids 1 to 414 of SEQ ID NO:55.

Figure 28 depicts the cDNA sequence and predicted amino acid sequence of rat 1p. The nucleotide sequence corresponds to nucleic acids 1 to 2643 of SEQ ID NO:56. The amino acid sequence corresponds to amino acids 1 to 267 of SEQ ID NO:57.

Figure 29 depicts the cDNA sequence and predicted amino acid sequence of rat 7s. The nucleotide sequence corresponds to nucleic acids 1 to 2929 of SEQ ID NO:58. The amino acid sequence corresponds to amino acids 1 to 270 of SEQ ID NO:59.

Figure 30 depicts the cDNA sequence and predicted amino acid sequence of rat 29x. The nucleotide sequence corresponds to nucleic acids 1 to 1489 of SEQ ID NO:60. The amino acid sequence corresponds to amino acids 1 to 351 of SEQ ID NO:61.

Figure 31 depicts the cDNA sequence of rat 25r. The nucleotide sequence corresponds to nucleic acids 1 to 1194 of SEQ ID NO:62.

Figure 32 depicts the cDNA sequence and predicted amino acid sequence of rat 5p. The nucleotide sequence corresponds to nucleic acids 1 to 600 of SEQ ID NO:63. The amino acid sequence corresponds to amino acids 1 to 95 of SEQ ID NO:64.

Figure 33 depicts the cDNA sequence and predicted amino acid sequence of rat 7q. The nucleotide sequence corresponds to nucleic acids 1 to 639 of SEQ ID NO:65. The amino acid sequence corresponds to amino acids 1 to 212 of SEQ ID NO:66.

Figure 34 depicts the cDNA sequence and predicted amino acid sequence of rat 19r. The nucleotide sequence corresponds to nucleic acids 1 to 816 of SEQ ID NO:67. The amino acid sequence corresponds to amino acids 1 to 271 of SEQ ID NO:68.

Figure 35 depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4c. The nucleotide sequence corresponds to nucleic acids 1 to 2263 of SEQ ID NO:69. The amino acid sequence corresponds to amino acids 1 to 229 of SEQ ID NO:70.

Figure 36 depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4d. The nucleotide sequence corresponds to nucleic acids 1 to 2259 of SEQ ID NO:71. The amino acid sequence corresponds to amino acids 1 to 250 of SEQ ID NO:72.

Figure 37 depicts an alignment of KChIP4a, KChIP4b, KChIP4c, and KChIP4d.

Figure 38 depicts a graph showing the current traces from CHO cells which express Kv4.2 with or without KChIP2 (9ql). Cells are voltage clamped at -80 mV and stepped from -60 mV to +50 mV for 200ms. Peak current amplitudes at the various test voltages are shown in the right panel. *Figure 38* further depicts a table showing the amplitude and kinetic effects of KChIP2 (9ql) on Kv4.2. KchIP2 expression alters the peak current amplitude, inactivation and recovery from inactivation time constants, and activation $V_{1/2}$.

Figure 39 depicts a graph showing the current traces from CHO cells which express Kv4.2 with or without KChIP3 (p19). Cells are voltage clamped at -80 mV and stepped

from -60 mV to +50 mV for 200ms. Peak current amplitudes at the various test voltages are shown in the right panel. *Figure 39* further depicts a table showing the amplitude and kinetic effects of KchIP3 (p19) on Kv4.2. KchIP3 causes alterations in peak current and inactivation and recovery from inactivation time constants.

Figure 40 depicts results from electrophysiological experiments demonstrating that coexpression of KChIP1 dramatically alters the current density and kinetics of Kv4.2 channels expressed in CHO cells.

Figure 40A depicts current traces from a Kv4.2 transfected CHO cell. Current was evoked by depolarizing the cell sequentially from a holding potential of -80 mV to test potentials from -60 to 50 mV. Current traces are leak subtracted using a p/5 protocol. The current axis is shown at the same magnification as in (b) to emphasize the change in current amplitudes. Inset- Single current trace at 50mV at an expanded current axis to show the kinetics of current activation and inactivation.

Figure 40B depicts current traces as in (a), but from a cell transfected with equal amounts of DNA for Kv4.2 and KChIP1.

Figure 40C depicts peak current amplitude at all voltages from cells transfected with Kv4.2 alone (n=11) or cotransfected with KChIP1 (n=9).

Figures 40D and 40E depict recovery from inactivation using a two pulse protocol. Kv4.2 alone (D) or coexpressed with KChIP1 (E) is driven into the inactivated state using a first pulse to 50 mV, then a second pulse to 50 mV is applied at varying times after the first pulse. Holding potential is -80 mV before and after all pulses.

Figure 40F depicts a summary of the percentage the peak current recovers between pulses for Kv4.2 (n=8) and Kv4.2 plus KChIP1 (n=5) transfected cells. The time constant of recovery from inactivation is fit to a single exponential.

Figure 41 depicts an alignment of human KChIP family members with closely related members of the recoverin family of Ca 2+ sensing proteins. (HIP:human hippocalcin; NCS1:rat neuronal calcium sensor 1). The alignment was performed using the MegAlign program for Macintosh (version 4.00 from DNASTAR) using the Clustal method with the PAM250 residue weight table and default parameters, and shaded using BOXSHADES. Residues identical to the consensus are shaded black, conservative substitutions are shaded grey. X, Y, Z and -X, -Y, -Z denote the positions of residues which are responsible for binding to the calcium ion in the EF hand.

Detailed Description of the Invention

The present invention is based, at least in part, on the discovery of novel nucleic acid molecules which encode gene products that interact with potassium channel proteins or possess substantial homology to the gene products of the invention that interact with potassium channel proteins (paralogs). Potassium channel proteins are, for example,

potassium channels having a Kv4.2 or Kv4.3 subunit. The nucleic acid molecules of the invention and their gene products are referred to herein as "Potassium Channel Interacting Proteins" "PCIP", or "KChIP" nucleic acid and protein molecules. The PCIP proteins of the present invention bind to and modulate a potassium channel mediated activity in a cell, e.g., a cardiac cell. Kv4 potassium channels, e.g., potassium channels having a Kv4.2 or Kv4.3 subunit, underlie the voltage-gated K+ current known as I_{to} (transient outward current) in the mammalian heart (Kaab S. *et al.* (1998) *Circulation* 98(14):1383-93; Dixon J.E. *et al.* (1996) *Circulation Research* 79(4):659-68; Nerbonne JM (1998) *Journal of Neurobiology* 37(1):37-59; Barry D.M. *et al.* (1998) *Circulation Research* 83(5):560-7; Barry D.M. *et al.* (1996) *Annual Review of Physiology* 58:363-94. This current underlies the rapid repolarization of cardiac myocytes during an action potential. It also participates in the inter-beat interval by controlling the rate at which cardiac myocytes reach the threshold for firing a subsequent action potential.

This current is also known to be down regulated in patients with cardiac hypertrophy, resulting in prolongation of the cardiac action potential. In these patients, action potential prolongation is thought to produce changes in calcium load and calcium handling within the myocardium, which contributes to the progression of cardiac disease from hypertrophy to heart failure (Wickenden *et al.* (1998) *Cardiovascular Research* 37:312). Interestingly, several PCIPs of the present invention (e.g., 9ql, 9qm, 9qs, shown in SEQ ID NOs:13, 15, 17, 19, 21, 23, and 25) bind to and modulate potassium channels containing a Kv4.2 or Kv4.3 subunit and contain calcium binding EF-hand domains. Because of mutations in these PCIP genes, defects in the expression of these calcium-binding PCIP proteins themselves, or defects in the interaction between these PCIPs and Kv4.2 or Kv4.3 channels, might be expected to lead to decreases in KV4.3 or Kv4.3(I_m) currents in the myocardium, therapeutic agents that alter PCIP expression or modulate the interaction between these PCIPs and Kv4.2 or Kv4.3 may be extremely valuable agents to slow or prevent the progression of disease from hypertrophy to heart failure.

Accordingly, in one aspect, this invention provides a method for identifying a compound suitable for treating a cardiovascular disorder by contacting a PCIP polypeptide, or a cell expressing a PCIP polypeptide with a test compound and determining whether the PCIP polypeptide binds to the test compound, thereby identifying a compound suitable for treating a potassium channel associated disorder such as a cardiovascular disorder. As used herein, a "potassium channel associated disorder" includes a disorder, disease or condition which is characterized by a misregulation of a potassium channel mediated activity. Potassium channel associated disorders can, for example, detrimentally affect the generation and distribution of electrical impulses that stimulate the cardiac muscle fibers to contract. Examples of potassium channel associated disorders include cardiovascular disorders such as arteriosclerosis, ischemia reperfusion injury, restenosis, arterial inflammation, vascular

wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrilation, long-QT syndrome, congestive heart failure, sinus node disfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia. In a preferred embodiment, the cardiovascular disorder is associated with an abnormal I_{to} current.

In a preferred embodiment, the binding of the test compound to the PCIP polypeptide is detected by direct detection of test compound/polypeptide binding. In another embodiment, the binding of the test compound to the PCIP polypeptide is detected by using a competition binding assay. In yet another embodiment, the binding of the test compound to the PCIP polypeptide is detected by using an assay for PCIP activity. As used interchangeably herein, a "PCIP activity", "biological activity of PCIP" or "functional activity of PCIP", refers to an activity exerted by a PCIP protein, polypeptide or nucleic acid molecule on a PCIP responsive cell or on a PCIP protein substrate, as determined *in vivo*, or *in vitro*, according to standard techniques. In one embodiment, a PCIP activity is a direct activity, such as an association with a PCIP-target molecule. As used herein, a "target molecule" or "binding partner" is a molecule with which a PCIP protein binds or interacts in nature, such that PCIP-mediated function is achieved. A PCIP target molecule can be a non-PCIP molecule or a PCIP protein or polypeptide. In an exemplary embodiment, a PCIP target molecule is a PCIP ligand. Alternatively, a PCIP activity is an indirect activity, such as a cellular signaling activity mediated by interaction of the PCIP protein with a PCIP ligand.

The biological activities of PCIP are described herein. For example, the binding of the test compound to the PCIP polypeptide is detected by using an assay for one or more of the following activities: (1) interaction with (e.g., binding to) a potassium channel protein or portion thereof, e.g., a potassium channel comprising a Kv4.3 or Kv4.2 subunit; (2) regulation of the phosphorylation state of a potassium channel protein or portion thereof; (3) association with (e.g., binding to) calcium and acting as a calcium dependent kinase; (4) modulation of a potassium channel mediated activity in a cell (e.g., a cardiac cell such as a pericardial cell, a myocardial cell, or an endocardial cell); (5) modulation of chromatin formation in a cell, e.g., a cardiac cell; (6) modulation of vesicular traffic and protein transport in a cell, e.g., a cardiac cell; (7) modulation of cytokine signaling in a cell, e.g., a cardiac cell; (8) regulation of the association of a potassium channel protein or portion thereof with the cellular cytoskeleton; (9) modulation of cellular proliferation; (10) modulation of the release of neurotransmitters; (11) modulation of membrane excitability; (12) influencing the resting potential of membranes; (13) modulation of wave forms and frequencies of action potentials; and (14) modulation of thresholds of excitation.

In another aspect, the invention features a method for identifying a compound suitable for treating a cardiovascular disorder by incubating a cell expressing a potassium channel or a fragment thereof, and a PCIP polypeptide, in the presence and absence of a candidate compound; and determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with the PCIP polypeptide, thereby identifying a compound suitable for treating a cardiovascular disorder. As used herein, a "potassium channel" includes a protein or polypeptide that is involved in receiving, conducting, and transmitting signals in an excitable cell. Potassium channels are typically expressed in electrically excitable cells, e.g., neurons, cardiac, skeletal and smooth muscle, renal, endocrine, and egg cells, and can form heteromultimeric structures, e.g., composed of pore-forming and cytoplasmic subunits. Examples of potassium channels include: (1) the voltage-gated potassium channels, (2) the ligand-gated potassium channels, and (3) the mechanically-gated potassium channels. For a detailed description of potassium channels, see Kandel E.R. et al., Principles of Neural Science, second edition, (Elsevier Science Publishing Co., Inc., N.Y. (1985)), the contents of which are incorporated herein by reference. The PCIP proteins of the present invention have been shown to interact with, for example, potassium channels having a Kv4.3 subunit or a Kv4.2 subunit.

In yet another aspect, the invention features a method for treating a cardiovascular disorder by contacting a potassium channel with an effective amount of a compound that modulates the binding of a PCIP protein to the potassium channel.

In a further aspect, the invention features a method for determining if a subject is at risk for a cardiovascular disorder by detecting, in a sample of cells from the subject an alteration in a PCIP gene which causes a mutated PCIP polypeptide to be produced, an alteration in a PCIP gene which causes abnormal expression of a PCIP polypeptide, or an alteration in a PCIP gene which causes abnormal processing of a PCIP polypeptide.

In another aspect, the invention features a method for identifying a subject suffering from a cardiovascular disorder by detecting, in a sample of cells from the subject an alteration in a PCIP gene which causes a mutated PCIP polypeptide to be produced, an alteration in a PCIP gene which causes abnormal expression of a PCIP polypeptide, or an alteration in a PCIP gene which causes abnormal processing of a PCIP polypeptide.

The PCIP molecules of the present invention were initially identified based on their ability, as determined using yeast two-hybrid assays (described in detail in Example 1), to interact with the amino-terminal 180 amino acids of rat Kv4.3 subunit. Further binding studies with other potassium subunits were performed to demonstrate specificity of the PCIP for Kv4.3 and Kv4.2. *In situ* localization, immuno-histochemical methods, co-immunoprecipitation and patch clamping methods were then used to clearly demonstrate that the PCIPs of the present invention interact with and modulate the activity of potassium channels, particularly those comprising a 4.3 or 4.2 subunit.

Several novel human, mouse, monkey, and rat PCIP family members have been identified, referred to herein as 1v, 9q, p19, W28559, KChIP4, 33b07, 1p, and rat 7s proteins and nucleic acid molecules. The human, rat, and mouse cDNAs encoding the 1v polypeptide are represented by SEQ ID NOs:1, 3, and 5, and shown in Figures 1, 2, and 3, respectively. In the brain, 1v mRNA is highly expressed in neocortical and hippocampal interneurons, in the thalamic reticular nucleus and medial habenula, in basal forebrain and striatal cholinergic neurons, in the superior colliculus, and in cerebellar granule cells. The 1v polypeptide is highly expressed in the somata, dendrites, axons and axon terminals of cells that express 1v mRNA. Splice variants of the 1v gene have been identified in rat and mouse and are represented by SEQ ID NOs: 7, 9, and 11 and shown in Figures 4, 5, and 6, respectively. 1v polypeptide interacts with potassium channels comprising Kv4.3 or kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot, the 1v transcripts (mRNA) are expressed predominantly in the brain

The 8t cDNA (SEQ ID NO: 29) encodes a polypeptide having a molecular weight of approximately 26 kD corresponding to SEQ ID NO:30 (see Figure 15). The 8t polypeptide interacts with potassium channel comprising Kv4.3 or Kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot and *in situ* data, the 8t mRNA is expressed predominantly in the heart and the brain. The 8t cDNA is a splice variant of 9q.

Human, rat, monkey, and mouse 9q cDNA was also isolated. Splice variants include human 9ql (SEQ ID NO:13; Figure 7) rat 9ql (SEQ ID NO:15; Figure 8), mouse 9ql (SEQ ID NO:17; Figure 9), human 9qm (SEQ ID NO:19; Figure 10), rat 9qm (SEQ ID NO:21; Figure 11), human 9qs (SEQ ID NO:23; Figure 12), monkey 9qs (SEQ ID NO:25; Figure 13), and rat 9qc (SEQ ID NO:27; Figure 14). The genomic DNA sequence of 9q has also be determined. Exon 1 and its flanking intron sequences (SEQ ID NO:46) are shown in Figure 22A. Exons 2-11 and the flanking intron sequences (SEQ ID NO:47) are shown in Figure 22B. 9q polypeptides interact with potassium channels comprising Kv4.3 or Kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot and *in situ* data, the 9q proteins are expressed predominantly in the heart and the brain. In the brain, 9q mRNA is highly expressed in the neostriatum, hippocampal formation, neocortical pyramidal cells and interneurons, and in the thalamus, superior colliculus, and cerebellum.

Human, rat, and mouse P19 cDNA were also isolated. Human P19 is shown in SEQ ID NO:31 and Figure 16; and in SEQ ID NO:39 and Figure 20 (the 3' sequence). Rat P19 is shown in SEQ ID NO:33 and Figure 17, and mouse P19 is shown in SEQ ID NO:35 and Figure 18. P19 polypeptides interact with potassium channels comprising Kv4.3 or Kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot analysis, the P19 transcripts (mRNA) are expressed predominantly in the brain and to a much lesser degree in the heart.

A partial human paralog of the PCIP molecules was also identified. This paralog is referred to herein as W28559 and is shown in SEQ ID NO:37 and Figure 19.

Monkey KChIP4a and its splice variants KChIP4b, KChIP4c, and KChIP4d were also identified. Monkey KChIP4a is shown in SEQ ID NO:48 and Figure 23. Monkey KChIP4b is shown in SEQ ID NO:50 and Figure 24. Monkey KChIP4c is shown in SEQ ID NO:69 and Figure 35. Monkey KChIP4d is shown in SEQ ID NO:71 and Figure 36.

The nucleotide sequence of the full length rat 33b07 cDNA and the predicted amino acid sequence of the rat 33b07 polypeptide are shown in Figure 26 and in SEQ ID NOs:52 and 53, respectively. The rat 33b07 cDNA encodes a protein having a molecular weight of approximately 44.7 kD and which is 407 amino acid residues in length. Rat 33b07 binds rKv4.3N and rKv4.2N with slight preference for rKv4.2N in yeast 2-hybrid assays.

The nucleotide sequence of the full length human 33b07 cDNA and the predicted amino acid sequence of the human 33b07 polypeptide are shown in Figure 27 and in SEQ ID NOs:54 and 55, respectively.

The nucleotide sequence of the partial length rat 1p cDNA and the predicted amino acid sequence of the rat 1p polypeptide are shown in Figure 28 and in SEQ ID NOs:56 and 57, respectively. The rat 1p cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 267 amino acid residues in length. Rat 1p binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays.

The nucleotide sequence of the partial length rat 7s cDNA and the predicted amino acid sequence of the rat 7s polypeptide are shown in Figure 29 and in SEQ ID NOs:58 and 59, respectively. The rat 7s cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 270 amino acid residues in length. Rat 7s binds rKv4.3N and rKv4.2N with preference for rKv4.3N in yeast two-hybrid assays.

The sequences of the PCIP molecules used in the methods of the present invention are summarized below, in Tables I and II.

Table I

PCIP Molecules Used in the Methods of the Present Invention

PCIP	Nucleic Acid Molecule Form	Source	SEQ ID NO: DNA	SEQ ID NO: PROTEIN	ATCC
1v or KChIP1	1v	human (225-875)*	1	2	98994

	1v	rat (210-860)	3	4	98946
	1v	mouse (477-1127)	5	6	98945
	1vl	rat (31-714)	7	8	98942
	1vl	mouse (77-760)	9	10	98943
	1vn (partial)	rat (345-955)	11	12	98944
9q or KChIP2	Genomic DNA sequence (Exon 1 and flanking intron sequences)	human	46		
	Genomic DNA sequence (Exons 2-11 and flanking intron sequences)	human	47		
	9ql	human (207-1019)	13	14	98993 98991
	9ql (partial)	rat (2-775)	15	16	98948
	9ql	mouse (181 -993)	17	18	98937
	9qm	human (207-965)	19	20	98993 98991
	9qm	rat (214-972)	21	22	98941
	9qs	human (207-869)	23	24	98951
	9qs	monkey (133-795)	25	26	98950
	9qc	rat (208-966)	27	28	98947

	8t (partial)	rat (1-678)	29	30	98939
p19 or KChIP3	p19	Human (1-771)	31	32	PTA-316
	p19 (partial)	rat (1-330)	33	34	98936
	p19	mouse (49-819)	35	36	98940
	p193 (partial)	Human (2-127)	39	40	98949
W28559	W28559 (partial)	human (1-339)	37	38	
KChIP4	KChIP4a	Monkey (265-966)	48	49	
	KChIP4b C-terminal splice variant	Monkey (265-966)	50	51	
	KChIP4c splice variant	Monkey (122-811)	69	70	
	KChIP4d splice variant	Monkey (64-816)	71	72	

* The coordinates of the coding sequence are shown in parenthesis. The first column indicates the PCIPs which were identified and column 2 indicates the various nucleic acid forms identified for each PCIP.

Table II

PCIP Molecules Used in the Methods of the Present Invention

PCIP	Nucleic Acid Molecule Form	Source	SEQ ID NO: DNA	SEQ ID NO: PROTEIN	ATCC
33b07 Novel	33b07	Human (88-1332)	52	53	PTA-316
	33b07	Rat (85-1308)	54	55	
1p Novel	1p (partial)	Rat (1-804)	56	57	

7s Novel	7s (partial)	Rat (1-813)	58	59	
29x	29x	Rat (433-1071)	60	61	
	25r splice variant of 29x	Rat (130-768)	62		
5p	5p	Rat (52-339)	63	64	
7q	7q	Rat (1-639)	65	66	
19r	19r	Rat (1-816)	67	68	

* The coordinates of the coding sequence are shown in parenthesis. The first column indicates the four families of PCIPs which were identified and column 2 indicates the various nucleic acid forms identified for each family. Novel molecules are also indicated.

Plasmids containing the nucleotide sequences encoding human, rat and monkey PCIPs were deposited with American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on November17, 1998, and assigned the Accession Numbers described above. These deposits will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. These deposits were made merely as a convenience for those of skill in the art and are not an admission that a deposit is required under 35 U.S.C. §112.

Clones containing cDNA molecules encoding human p19 (clone EphP19) and human 33b07 (clone Eph33b07) were deposited with American Type Culture Collection (Manassas, VA) on July 8,1998 as Accession Number PTA-316, as part of a composite deposit representing a mixture of two strains, each carrying one recombinant plasmid harboring a particular cDNA clone. (The ATCC strain designation for the mixture of hP19 and h33b07 is EphP19h33b07mix).

To distinguish the strains and isolate a strain harboring a particular cDNA clone, an aliquot of the mixture can be streaked out to single colonies on LB plates supplemented with 100 ug/ml ampicillin, single colonies grown, and then plasmid DNA extracted using a standard minipreparation procedure. Next, a sample of the DNA minipreparation can be digested with NotI and the resultant products resolved on a 0.8% agarose gel using standard DNA electrophoresis conditions. The digest gives the following band patterns: EphP19: 7 kb 9 (single band), Eph33b07: 5.8 kb (single band).

Various aspects of the invention are described in further detail in the following subsections:

I. Screening Assays:

The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, i.e., candidate or test compounds or agents (e.g., peptides, peptidomimetics, small molecules or other drugs) which bind to PCIP proteins, have a stimulatory or inhibitory effect on, for example, PCIP expression or PCIP activity, or have a stimulatory or inhibitory effect on, for example, the expression or activity of a PCIP substrate.

In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a PCIP protein or polypeptide or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a PCIP protein or polypeptide or biologically active portion thereof. The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. (1997) *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann et al. (1994). *J. Med. Chem.* 37:2678; Cho et al. (1993) *Science* 261:1303; Carrell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop et al. (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (e.g., Houghten (1992) *Biotechniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (Ladner USP 5,223,409), spores (Ladner USP '409), plasmids (Cull et al. (1992) *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith (1990) *Science* 249:386-390); (Devlin (1990) *Science* 249:404-406); (Cwirla et al. (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382); (Felici (1991) *J. Mol. Biol.* 222:301-310); (Ladner *supra.*).

In one embodiment, an assay is a cell-based assay in which a cell which expresses a PCIP protein or biologically active portion thereof is contacted with a test compound and the

ability of the test compound to modulate PCIP activity, e.g., binding to a potassium channel comprising a Kv4.2 or Kv4.2 subunit, or a portion thereof, is determined. Determining the ability of the test compound to modulate PCIP activity can be accomplished by monitoring, for example, the I_{to} current or the release of a neurotransmitter from a cell which expresses PCIP such as a cardiac cell. Currents in cells, e.g., the I_{to} current, can be measured using the patch-clamp technique as described in the Examples section using the techniques described in, for example, Hamill et al. 1981. Pfluegers Arch. 391: 85-100). The cell, for example, can be of mammalian origin. Determining the ability of the test compound to modulate the ability of PCIP to bind to a substrate can be accomplished, for example, by coupling the PCIP substrate with a radioisotope or enzymatic label such that binding of the PCIP substrate to PCIP can be determined by detecting the labeled PCIP substrate in a complex. For example, compounds (e.g., PCIP substrates) can be labeled with ^{125}I, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemmission or by scintillation counting. Alternatively, compounds can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

It is also within the scope of this invention to determine the ability of a compound (e.g., PCIP substrate) to interact with PCIP without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a compound with PCIP without the labeling of either the compound or the PCIP. McConnell, H. M. et al. (1992) *Science* 257:1906-1912. As used herein, a "microphysiometer" (e.g., Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and PCIP.

In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a PCIP target molecule (e.g., a potassium channel comprising a Kv4.2 or Kv4.2 subunit, or a portion thereof, is determined. Determining the ability of the test compound to modulate, or a fragment thereof) with a test compound and determining the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the PCIP target molecule. Determining the ability of the test compound to modulate the activity of a PCIP target molecule can be accomplished, for example, by determining the ability of the PCIP protein to bind to or interact with the PCIP target molecule, e.g., a potassium channel or a fragment thereof.

Determining the ability of the PCIP protein or a biologically active fragment thereof, to bind to or interact with a PCIP target molecule can be accomplished by one of the methods described above for determining direct binding. In a preferred embodiment, determining the ability of the PCIP protein to bind to or interact with a PCIP target molecule

can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (i.e., intracellular Ca^{2+}, diacylglycerol, IP_3, and the like), detecting catalytic/enzymatic activity of the target an appropriate substrate, detecting the induction of a reporter gene (comprising a target-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, e.g., luciferase), or detecting a target-regulated cellular response such as the release of a neurotransmitter.

In yet another embodiment, an assay of the present invention is a cell-free assay in which a PCIP protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to bind to the PCIP protein or biologically active portion thereof is determined. Preferred biologically active portions of the PCIP proteins to be used in assays of the present invention include fragments which participate in interactions with non-PCIP molecules, e.g., potassium channels comprising a Kv4.2 or Kv4.2 subunit, or a portion thereof, is determined. Determining the ability of the test compound to modulate, or fragments thereof, or fragments with high surface probability scores. Binding of the test compound to the PCIP protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the PCIP protein or biologically active portion thereof with a known compound which binds PCIP to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a PCIP protein, wherein determining the ability of the test compound to interact with a PCIP protein comprises determining the ability of the test compound to preferentially bind to PCIP or biologically active portion thereof as compared to the known compound.

In another embodiment, the assay is a cell-free assay in which a PCIP protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the PCIP protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate the activity of a PCIP protein can be accomplished, for example, by determining the ability of the PCIP protein to bind to a PCIP target molecule by one of the methods described above for determining direct binding. Determining the ability of the PCIP protein to bind to a PCIP target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA). Sjolander, S. and Urbaniczky, C. (1991) *Anal. Chem.* 63:2338-2345 and Szabo et al. (1995) *Curr. Opin. Struct. Biol.* 5:699-705. As used herein, "BIA" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g., BIAcore). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

In an alternative embodiment, determining the ability of the test compound to modulate the activity of a PCIP protein can be accomplished by determining the ability of the PCIP protein to further modulate the activity of a downstream effector of a PCIP target molecule. For example, the activity of the effector molecule on an appropriate target can be determined or the binding of the effector to an appropriate target can be determined as previously described.

In yet another embodiment, the cell-free assay involves contacting a PCIP protein or biologically active portion thereof with a known compound which binds the PCIP protein to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the PCIP protein, wherein determining the ability of the test compound to interact with the PCIP protein comprises determining the ability of the PCIP protein to preferentially bind to or modulate the activity of a PCIP target molecule.

The cell-free assays of the present invention are amenable to use of both soluble and/or membrane-bound forms of isolated proteins. In the case of cell-free assays in which a membrane-bound form of an isolated protein is used (e.g., a potassium channel) it may be desirable to utilize a solubilizing agent such that the membrane-bound form of the isolated protein is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton® X-100, Triton® X-114, Thesit®, Isotridecypoly(ethylene glycol ether)$_n$, 3-[(3-cholamidopropyl)dimethylamminio]-1-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl)dimethylamminio]-2-hydroxy-1-propane sulfonate (CHAPSO), or N-dodecyl=N,N-dimethyl-3-ammonio-1-propane sulfonate.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either PCIP or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a PCIP protein, or interaction of a PCIP protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/ PCIP fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or PCIP protein, and the mixture incubated under conditions conducive to complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are

washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of PCIP binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a PCIP protein or a PCIP target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated PCIP protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with PCIP protein or target molecules but which do not interfere with binding of the PCIP protein to its target molecule can be derivatized to the wells of the plate, and unbound target or PCIP protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the PCIP protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the PCIP protein or target molecule.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate vesicular traffic and protein transport in a cell, e.g., a cardiac cell, using the assays described in, for example, Komada M. *et al.* (1999) *Genes Dev.*13(11):1475-85, and Roth M.G. *et al.* (1999) *Chem. Phys. Lipids.* 98(1-2):141-52, the contents of which are incorporated herein by reference.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to regulate the phosphorylation state of a potassium channel protein or portion thereof, using for example, an *in vitro* kinase assay. Briefly, a PCIP target molecule, e.g., an immunoprecipitated potassium channel from a cell line expressing such a molecule, can be incubated with the PCIP protein and radioactive ATP, e.g., [γ-^{32}P] ATP, in a buffer containing $MgCl_2$ and $MnCl_2$, e.g., 10 mM $MgCl_2$ and 5 mM $MnCl_2$. Following the incubation, the immunoprecipitated PCIP target molecule, e.g., the potassium channel, can be separated by SDS-polyacrylamide gel electrophoresis under reducing conditions, transferred to a membrane, e.g., a PVDF membrane, and autoradiographed. The appearance of detectable bands on the autoradiograph indicates that the PCIP substrate, e.g., the potassium channel, has been phosphorylated. Phosphoaminoacid analysis of the phosphorylated substrate can also be performed in order to determine which residues on the PCIP substrate are phosphorylated. Briefly, the radiophosphorylated protein band can be excised from the SDS gel and subjected to partial acid hydrolysis. The products can then be separated by one-

dimensional electrophoresis and analyzed on, for example, a phosphoimager and compared to ninhydrin-stained phosphoaminoacid standards. Assays such as those described in, for example, Tamaskovic R. *et al.* (1999) *Biol. Chem.* 380(5):569-78, the contents of which are incorporated herein by reference, can also be used.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to associate with (e.g., bind) calcium, using for example, the assays described in Liu L. (1999) *Cell Signal.* 11(5):317-24 and Kawai T. *et al.* (1999) *Oncogene* 18(23):3471-80, the contents of which are incorporated herein by reference.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate chromatin formation in a cell, using for example, the assays described in Okuwaki M. *et al.* (1998) *J. Biol. Chem.* 273(51):34511-8 and Miyaji-Yamaguchi M. (1999) J. Mol. Biol. 290(2): 547-557, the contents of which are incorporated herein by reference.

In yet another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate cellular proliferation, using for example, the assays described in Baker F.L. *et al.* (1995) *Cell Prolif.* 28(1):1-15, Cheviron N. *et al.* (1996) *Cell Prolif.* 29(8):437-46, Hu Z.W. *et al.* (1999) *J. Pharmacol. Exp. Ther.* 290(1):28-37 and Elliott K. *et al.* (1999) *Oncogene* 18(24):3564-73, the contents of which are incorporated herein by reference.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to regulate the association of a potassium channel protein or portion thereof with the cellular cytoskeleton, using for example, the assays described in Gonzalez C. *et al.* (1998) *Cell Mol. Biol.* 44(7):1117-27and Chia C.P. *et al.* (1998) *Exp. Cell Res.*244(1):340-8, the contents of which are incorporated herein by reference.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate membrane excitability, using for example, the assays described in Bar-Sagi D. *et al.* (1985) *J. Biol. Chem.* 260(8):4740-4 and Barker J.L. *et al.* (1984) *Neurosci. Lett.* 47(3):313-8, the contents of which are incorporated herein by reference.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate cytokine signaling in a cell, e.g., a cardiac cell, the assays described in Nakashima Y. *et al.* (1999) *J. Bone Joint Surg. Am.* 81(5):603-15, the contents of which are incorporated herein by reference.

In another embodiment, modulators of PCIP expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of PCIP mRNA

or protein in the cell is determined. The level of expression of PCIP mRNA or protein in the presence of the candidate compound is compared to the level of expression of PCIP mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of PCIP expression based on this comparison. For example, when expression of PCIP mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of PCIP mRNA or protein expression. Alternatively, when expression of PCIP mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of PCIP mRNA or protein expression. The level of PCIP mRNA or protein expression in the cells can be determined by methods described herein for detecting PCIP mRNA or protein.

In yet another aspect of the invention, the PCIP proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, e.g., U.S. Patent No. 5,283,317; Zervos et al. (1993) *Cell* 72:223-232; Madura et al. (1993) *J. Biol. Chem.* 268:12046-12054; Bartel et al. (1993) *Biotechniques* 14:920-924; Iwabuchi et al. (1993) *Oncogene* 8:1693-1696; and Brent WO94/10300), to identify other proteins, which bind to or interact with PCIP ("PCIP-binding proteins" or "PCIP-bp") and are involved in PCIP activity (described in more detail in the Examples section below). Such PCIP-binding proteins are also likely to be involved in the propagation of signals by the PCIP proteins or PCIP targets as, for example, downstream elements of a PCIP-mediated signaling pathway. Alternatively, such PCIP-binding proteins are likely to be PCIP inhibitors.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a PCIP protein is fused to a gene encoding the DNA binding domain of a known transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo,* forming a PCIP-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (e.g., LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the PCIP protein.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent

identified as described herein in an appropriate animal model. For example, an agent identified as described herein (e.g., a PCIP modulating agent, an antisense PCIP nucleic acid molecule, a PCIP-specific antibody, or a PCIP-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

II. Predictive Medicine:

The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining PCIP protein and/or nucleic acid expression as well as PCIP activity, in the context of a biological sample (e.g., blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant PCIP expression or activity. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with PCIP protein, nucleic acid expression or activity. For example, mutations in a PCIP gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby phophylactically treat an individual prior to the onset of a disorder characterized by or associated with PCIP protein, nucleic acid expression or activity.

Another aspect of the invention pertains to monitoring the influence of agents (e.g., drugs, compounds) on the expression or activity of PCIP in clinical trials.

These and other agents are described in further detail in the following sections.

1. Diagnostic Assays

An exemplary method for detecting the presence or absence of PCIP protein or nucleic acid in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting PCIP protein or nucleic acid (e.g., mRNA, genomic DNA) that encodes PCIP protein such that the presence of PCIP protein or nucleic acid is detected in the biological sample. A preferred agent for detecting PCIP mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to PCIP mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length PCIP nucleic acid, such as the nucleic acid of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID

NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to PCIP mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

A preferred agent for detecting PCIP protein is an antibody capable of binding to PCIP protein, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (e.g., Fab or $F(ab')_2$) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect PCIP mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of PCIP mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of PCIP protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of PCIP genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of PCIP protein include introducing into a subject a labeled anti-PCIP antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the test subject. Alternatively, the biological sample can contain mRNA molecules from the test subject or genomic DNA molecules from the test subject. A preferred biological sample is a serum sample isolated by conventional means from a subject.

In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting PCIP protein, mRNA, or genomic DNA, such that the presence of PCIP

protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of PCIP protein, mRNA or genomic DNA in the control sample with the presence of PCIP protein, mRNA or genomic DNA in the test sample.

The invention also encompasses kits for detecting the presence of PCIP in a biological sample. For example, the kit can comprise a labeled compound or agent capable of detecting PCIP protein or mRNA in a biological sample; means for determining the amount of PCIP in the sample; and means for comparing the amount of PCIP in the sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect PCIP protein or nucleic acid.

2. Prognostic Assays

The diagnostic methods described herein can furthermore be utilized to identify subjects having or at risk of developing a disease or disorder associated with aberrant PCIP expression or activity. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or at risk of developing a disorder associated with a misregulation in PCIP protein activity or nucleic acid expression, such as a cardiovascular disorders such as sinus node disfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrythmia.

Alternatively, the prognostic assays can be utilized to identify a subject having or at risk for developing a disorder associated with a misregulation in PCIP protein activity or nucleic acid expression, such as a potassium channel associated disorder. Thus, the present invention provides a method for identifying a disease or disorder associated with aberrant PCIP expression or activity in which a test sample is obtained from a subject and PCIP protein or nucleic acid (e.g., mRNA or genomic DNA) is detected, wherein the presence of PCIP protein or nucleic acid is diagnostic for a subject having or at risk of developing a disease or disorder associated with aberrant PCIP expression or activity. As used herein, a "test sample" refers to a biological sample obtained from a subject of interest. For example, a test sample can be a biological fluid (e.g., serum), cell sample, or tissue.

Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant PCIP expression or activity. For example, such methods can be used to determine whether a subject can be effectively treated with an agent for a cardiovascular disorder. Thus, the present invention provides methods for determining whether a subject can be effectively treated with an agent for a disorder associated with aberrant PCIP expression or activity in which a test sample is obtained and PCIP protein or

nucleic acid expression or activity is detected (e.g., wherein the abundance of PCIP protein or nucleic acid expression or activity is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant PCIP expression or activity).

The methods of the invention can also be used to detect genetic alterations in a PCIP gene, thereby determining if a subject with the altered gene is at risk for a disorder characterized by misregulation in PCIP protein activity or nucleic acid expression, such as a cardiovascular disorder. In preferred embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a genetic alteration characterized by at least one of an alteration affecting the integrity of a gene encoding a PCIP-protein, or the mis-expression of the PCIP gene. For example, such genetic alterations can be detected by ascertaining the existence of at least one of 1) a deletion of one or more nucleotides from a PCIP gene; 2) an addition of one or more nucleotides to a PCIP gene; 3) a substitution of one or more nucleotides of a PCIP gene, 4) a chromosomal rearrangement of a PCIP gene; 5) an alteration in the level of a messenger RNA transcript of a PCIP gene, 6) aberrant modification of a PCIP gene, such as of the methylation pattern of the genomic DNA, 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of a PCIP gene, 8) a non-wild type level of a PCIP-protein, 9) allelic loss of a PCIP gene, and 10) inappropriate post-translational modification of a PCIP-protein. As described herein, there are a large number of assays known in the art which can be used for detecting alterations in a PCIP gene. A preferred biological sample is a tissue or serum sample isolated by conventional means from a subject.

In certain embodiments, detection of the alteration involves the use of a probe/primer in a polymerase chain reaction (PCR) (see, e.g., U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran et al. (1988) *Science* 241:1077-1080; and Nakazawa et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:360-364), the latter of which can be particularly useful for detecting point mutations in the PCIP-gene (see Abravaya et al. (1995) *Nucleic Acids Res* .23:675-682). This method can include the steps of collecting a sample of cells from a subject, isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a PCIP gene under conditions such that hybridization and amplification of the PCIP-gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication (Guatelli, J.C. et al., (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh, D.Y. et al., (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177),

Q-Beta Replicase (Lizardi, P.M. et al. (1988) *Bio-Technology* 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In an alternative embodiment, mutations in a PCIP gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (see, for example, U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

In other embodiments, genetic mutations in PCIP can be identified by hybridizing a sample and control nucleic acids, e.g., DNA or RNA, to high density arrays containing hundreds or thousands of oligonucleotides probes (Cronin, M.T. et al. (1996) *Human Mutation* 7: 244-255; Kozal, M.J. et al. (1996) *Nature Medicine* 2: 753-759). For example, genetic mutations in PCIP can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, M.T. *et al. supra.* Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification of point mutations. This step is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the PCIP gene and detect mutations by comparing the sequence of the sample PCIP with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxam and Gilbert ((1977) *Proc. Natl. Acad. Sci. USA* 74:560) or Sanger ((1977) *Proc. Natl. Acad. Sci. USA* 74:5463). It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays ((1995) *Biotechniques* 19:448), including sequencing by mass spectrometry (see, e.g., PCT International Publication No. WO 94/16101; Cohen et al. (1996) *Adv. Chromatogr.* 36:127-162; and Griffin et al. (1993) *Appl. Biochem. Biotechnol.* 38:147-159).

Other methods for detecting mutations in the PCIP gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or

RNA/DNA heteroduplexes (Myers et al. (1985) *Science* 230:1242). In general, the art technique of "mismatch cleavage" starts by providing heteroduplexes of formed by hybridizing (labeled) RNA or DNA containing the wild-type PCIP sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S1 nuclease to enzymatically digesting the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. See, for example, Cotton *et al.* (1988) *Proc. Natl Acad Sci USA* 85:4397; Saleeba et al. (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in PCIP cDNAs obtained from samples of cells. For example, the mutY enzyme of E. coli cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches (Hsu *et al.* (1994) *Carcinogenesis* 15:1657-1662). According to an exemplary embodiment, a probe based on a PCIP sequence, e.g., a wild-type PCIP sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. See, for example, U.S. Patent No. 5,459,039.

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in PCIP genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita *et al.* (1989) *Proc Natl. Acad. Sci USA*: 86:2766, see also Cotton (1993) *Mutat. Res.* 285:125-144; and Hayashi (1992) *Genet. Anal. Tech. Appl.* 9:73-79). Single-stranded DNA fragments of sample and control PCIP nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double

stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen et al. (1991) *Trends Genet* 7:5).

In yet another embodiment the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers *et al.* (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys Chem* 265:12753).

Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki *et al.* (1986) *Nature* 324:163); Saiki *et al.* (1989) *Proc. Natl Acad. Sci USA* 86:6230). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs *et al.* (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini *et al.* (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein, which may be conveniently used, *e.g.,* in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving a PCIP gene.

Furthermore, any cell type or tissue in which PCIP is expressed may be utilized in the prognostic assays described herein.

3. Monitoring of Effects During Clinical Trials

Monitoring the influence of agents (e.g., drugs) on the expression or activity of a PCIP protein (e.g., the modulation of membrane excitability or resting potential) can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent determined by a screening assay as described herein to increase PCIP gene expression, protein levels, or upregulate PCIP activity, can be monitored in clinical trials of subjects exhibiting decreased PCIP gene expression, protein levels, or downregulated PCIP activity. Alternatively, the effectiveness of an agent determined by a screening assay to decrease PCIP gene expression, protein levels, or downregulate PCIP activity, can be monitored in clinical trials of subjects exhibiting increased PCIP gene expression, protein levels, or upregulated PCIP activity. In such clinical trials, the expression or activity of a PCIP gene, and preferably, other genes that have been implicated in, for example, a potassium channel associated disorder can be used as a "read out" or markers of the phenotype of a particular cell.

For example, and not by way of limitation, genes, including PCIP, that are modulated in cells by treatment with an agent (e.g., compound, drug or small molecule) which modulates PCIP activity (e.g., identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents on potassium channel associated disorders, for example, in a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of PCIP and other genes implicated in the potassium channel associated disorder, respectively. The levels of gene expression (e.g., a gene expression pattern) can be quantified by northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods as described herein, or by measuring the levels of activity of PCIP or other genes. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during treatment of the individual with the agent.

In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate identified by the screening assays described herein) including the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of a PCIP protein, mRNA, or genomic DNA in the preadministration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of the PCIP protein, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity of the PCIP protein, mRNA, or genomic DNA in the pre-administration sample with the PCIP protein, mRNA, or genomic DNA in the post administration sample or samples; and (vi)

altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of PCIP to higher levels than detected, i.e., to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of PCIP to lower levels than detected, i.e. to decrease the effectiveness of the agent. According to such an embodiment, PCIP expression or activity may be used as an indicator of the effectiveness of an agent, even in the absence of an observable phenotypic response.

III. Methods of Treatment:

The present invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant PCIP expression or activity such as a cardiovascular disorder. With regard to both prophylactic and therapeutic methods of treatment, such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics. "Pharmacogenomics", as used herein, refers to the application of genomics technologies such as gene sequencing, statistical genetics, and gene expression analysis to drugs in clinical development and on the market. More specifically, the term refers the study of how a patient's genes determine his or her response to a drug (e.g., a patient's "drug response phenotype", or "drug response genotype".) Thus, another aspect of the invention provides methods for tailoring an individual's prophylactic or therapeutic treatment with either the PCIP molecules of the present invention or PCIP modulators according to that individual's drug response genotype. Pharmacogenomics allows a clinician or physician to target prophylactic or therapeutic treatments to patients who will most benefit from the treatment and to avoid treatment of patients who will experience toxic drug-related side effects.

1. Prophylactic Methods

In one aspect, the invention provides a method for preventing in a subject, a disease or condition associated with an aberrant PCIP expression or activity such as a cardiovascular disorder, by administering to the subject a PCIP or an agent which modulates PCIP expression or at least one PCIP activity. Subjects at risk for a disease which is caused or contributed to by aberrant PCIP expression or activity can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the PCIP aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending on the type of PCIP aberrancy, for example, a PCIP, PCIP agonist or PCIP antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein.

2. Therapeutic Methods

Another aspect of the invention pertains to methods of modulating PCIP expression or activity for therapeutic purposes. Accordingly, in an exemplary embodiment, the modulatory method of the invention involves contacting a cell with a PCIP or agent that modulates one or more of the activities of PCIP protein activity associated with the cell. An agent that modulates PCIP protein activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring target molecule of a PCIP protein (e.g., a PCIP substrate), a PCIP antibody, a PCIP agonist or antagonist, a peptidomimetic of a PCIP agonist or antagonist, or other small molecule. In one embodiment, the agent stimulates one or more PCIP activities. Examples of such stimulatory agents include active PCIP protein and a nucleic acid molecule encoding PCIP that has been introduced into the cell. In another embodiment, the agent inhibits one or more PCIP activities. Examples of such inhibitory agents include antisense PCIP nucleic acid molecules, anti-PCIP antibodies, and PCIP inhibitors. These modulatory methods can be performed *in vitro* (e.g., by culturing the cell with the agent) or, alternatively, *in vivo* (e.g., by administering the agent to a subject). As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant expression or activity of a PCIP protein or nucleic acid molecule. Examples of such disorders include cardiovascular disorders such as long-QT syndrome, sinus node disfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrythmia. In one embodiment, the method involves administering an agent (e.g., an agent identified by a screening assay described herein), or combination of agents that modulates (e.g., upregulates or downregulates) PCIP expression or activity. In another embodiment, the method involves administering a PCIP protein or nucleic acid molecule as therapy to compensate for reduced or aberrant PCIP expression or activity.

Stimulation of PCIP activity is desirable in situations in which PCIP is abnormally downregulated and/or in which increased PCIP activity is likely to have a beneficial effect. For example, stimulation of PCIP activity is desirable in situations in which a PCIP is downregulated and/or in which increased PCIP activity is likely to have a beneficial effect. Likewise, inhibition of PCIP activity is desirable in situations in which PCIP is abnormally upregulated and/or in which decreased PCIP activity is likely to have a beneficial effect.

A PCIP molecule or an agent that modulates one or more of the activities of PCIP protein activity associated with the cell can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and

absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

A pharmaceutical composition used in the methods of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (e.g., a fragment of a PCIP protein or an anti-PCIP antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The pharmaceutical compositions used in the methods of the invention can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, pharmaceutical compositions used in the methods of the invention are prepared with carriers that will protect the active compound against rapid elimination from the body, such as a controlled release formulation, including implants and

microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.,* for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

As defined herein, a therapeutically effective amount of protein or polypeptide (i.e., an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

In a preferred example, a subject is treated with antibody, protein, or polypeptide in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of antibody, protein, or polypeptide used for treatment may increase or decrease over the course of a particular treatment. Changes in dosage may result and become apparent from the results of diagnostic assays as described herein.

The methods of the present invention encompasses the use of agents which modulate expression or activity. An agent may, for example, be a small molecule. For example, such small molecules include, but are not limited to, peptides, peptidomimetics, amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (i.e,. including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds. It is understood that appropriate doses of small molecule agents depends upon a number of factors within the ken of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of the small molecule will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the small molecule to have upon the nucleic acid or polypeptide of the invention. Exemplary doses include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (e.g., about 1microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1microgram per kilogram to about 50 micrograms per kilogram. It is

furthermore understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. Such appropriate doses may be determined using the assays described herein. When one or more of these small molecules is to be administered to an animal (e.g., a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

Further, an antibody (or fragment thereof) may be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, .alpha.-interferon, .beta.-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophase colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982). Alternatively, an antibody can be conjugated to a second antibody to Form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

The nucleic acid molecules used in the methods of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (see U.S. Patent 5,328,470) or by stereotactic injection (see e.g., Chen et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g., retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

3. Pharmacogenomics

The PCIP molecules of the present invention, as well as agents, or modulators which have a stimulatory or inhibitory effect on PCIP activity (e.g., PCIP gene expression) as identified by a screening assay described herein can be administered to individuals to treat (prophylactically or therapeutically) potassium channel associated disorders associated with aberrant PCIP activity (e.g, cardiovascular disorders such as long-QT syndrome, sinus node disfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrythmia). In conjunction with such treatment, pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant

pharmacogenomics studies in determining whether to administer a PCIP molecule or PCIP modulator as well as tailoring the dosage and/or therapeutic regimen of treatment with a PCIP molecule or PCIP modulator.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, for example, Eichelbaum, M. et al. (1996) *Clin. Exp. Pharmacol. Physiol.* 23(10-11) :983-985 and Linder, M.W. et al. (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare genetic defects or as naturally-occurring polymorphisms. For example, glucose-6-phosphate dehydrogenase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is haemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

One pharmacogenomics approach to identifying genes that predict drug response, known as "a genome-wide association", relies primarily on a high-resolution map of the human genome consisting of already known gene-related markers (e.g., a "bi-allelic" gene marker map which consists of 60,000-100,000 polymorphic or variable sites on the human genome, each of which has two variants.) Such a high-resolution genetic map can be compared to a map of the genome of each of a statistically significant number of patients taking part in a Phase II/III drug trial to identify markers associated with a particular observed drug response or side effect. Alternatively, such a high resolution map can be generated from a combination of some ten-million known single nucleotide polymorphisms (SNPs) in the human genome. As used herein, a "SNP" is a common alteration that occurs in a single nucleotide base in a stretch of DNA. For example, a SNP may occur once per every 1000 bases of DNA. A SNP may be involved in a disease process, however, the vast majority may not be disease-associated. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In such a manner, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that may be common among such genetically similar individuals.

Alternatively, a method termed the "candidate gene approach", can be utilized to identify genes that predict drug response. According to this method, if a gene that encodes a drugs target is known (e.g., a PCIP protein of the present invention), all common variants of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (e.g., N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Alternatively, a method termed the "gene expression profiling", can be utilized to identify genes that predict drug response. For example, the gene expression of an animal dosed with a drug (e.g., a PCIP molecule or PCIP modulator of the present invention) can give an indication whether gene pathways related to toxicity have been turned on.

Information generated from more than one of the above pharmacogenomics approaches can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment an individual. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a PCIP molecule or PCIP modulator, such as a modulator identified by one of the exemplary screening assays described herein.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figures and the Sequence Listing are incorporated herein by reference.

EXAMPLES

The following materials and methods were used in the Examples.

Strains, plasmids, bait cDNAs, and general microbiological techniques

Basic yeast strains (HF7c, Y187,) bait (pGBT9) and fish (pACT2) plasmids used in this work were purchased from Clontech (Palo Alto, CA). cDNAs encoding rat Kv4.3, Kv4.2, and Kv1.1, were provided by Wyeth-Ayerst Research (865 Ridge Rd., Monmouth Junction, NJ 08852) Standard yeast media including synthetic complete medium lacking L-leucine, L-tryptophan, and L-histidine were prepared and yeast genetic manipulations were performed as described (Sherman (1991) *Meth. Enzymol.* 194:3-21). Yeast transformations were performed using standard protocols (Gietz et al. (1992) *Nucleic Acids Res.* 20:1425; Ito et al (1983) *J. Bacteriol.* 153:163-168). Plasmid DNAs were isolated from yeast strains by a standard method (Hoffman and Winston (1987) *Gene* 57:267-272).

Bait and Yeast Strain Construction

The first 180 amino acids of rKv4.3 (described in Serdio P. et al. (1996) *J. Neurophys* 75:2174-2179) were amplified by PCR and cloned in frame into pGBT9 resulting in plasmid pFWA2, (hereinafter "bait"). This bait was transformed into the two-hybrid screening strain HF7c and tested for expression and self-activation. The bait was validated for expression by Western blotting. The rKv4.3 bait did not self-activate in the presence of 10 mM 3-amino-1,2,3-Triazole (3-AT).

Library construction

Rat mid brain tissue was provided by Wyeth-Ayerst Research (Monmouth Junction, NJ). Total cellular RNA was extracted from the tissues using standard techniques (Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989)). mRNA was prepared using a Poly-A Spin mRNA Isolation Kit from New England Biolabs (Beverly, MA). cDNA from the mRNA sample was synthesized using a cDNA Synthesis Kit from Stratagene (La Jolla, CA) and ligated into pACT2's EcoRI and XhoI sites, giving rise to a two-hybrid library.

Two-Hybrid Screening

Two-hybrid screens were carried out essentially as described in Bartel, P. et al. (1993) "Using the Two-Hybrid System to Detect Polypeptide-Polypeptide Interactions" *in* Cellular Interactions in Development: A Practical Approach, Hartley, D.A. ed. Oxford University Press, Oxford, pp. 153-179, with a bait-library pair of rkv4.3 bait-rat mid brain library. A filter disk beta-galactosidase (beta-gal) assay was performed essentially as

previously described (Brill et al. (1994) *Mol. Biol. Cell.* 5:297-312). Clones that were positive for both reporter gene activity (His and beta-galactosidase) were scored and fish, plasmids were isolated from yeast, transformed into *E. coli* strain KC8, DNA plasmids were purified and the resulting plasmids were sequenced by conventional methods (Sanger F. et al. (1977) *PNAS*, 74: 5463-67).

Specificity test

Positive interactor clones were subjected to a binding specificity test where they were exposed to a panel of related and unrelated baits by a mating scheme previously described (Finley R.L. Jr. et al. (1994) *PNAS*, 91(26):12980-12984). Briefly, positive fish plasmids were transformed into Y187 and the panel of baits were transformed into HF7c. Transformed fish and bait cells were streaked out as stripes on selective medium plates, mated on YPAD plates, and tested for reporter gene activity.

Analysis

PCIP nuleotides were analyzed for nucleic acid hits by the BLASTN 1.4.8MP program (Altschul et al. (1990) Basic Local Alignment Search Tool. *J. Mol. Biol.* 215: 403-410). PCIP proteins were analyzed for polypeptide hits by the BLASTP 1.4.9MP program.

EXAMPLE 1: IDENTIFICATION OF RAT PCIP cDNAs

The Kv4.3 gene coding sequence (coding for the first 180 amino acids) was amplified by PCR and cloned into pGBT9 creating a GAL4 DNA-binding domain-Kv4.3(1-180) gene fusion (plasmid pFWA2). HF7c was transformed with this construct. The resulting strain grew on synthetic complete medium lacking L-tryptophan but not on synthetic complete medium lacking L-tryptophan and L-histidine in the presence of 10mM 3-AT demonstrating that the {GAL4 DNA-binding domain}-{vKv4.3(1-180)} gene fusion does not have intrinsic transcriptional activation activity higher than the threshhold allowed by 10mM 3-AT .

In this example, a yeast two-hybrid assay was performed in which a plasmid containing a {GAL4 DNA-binding domain}-{rKv4.3(1-180)} gene fusion was introduced into the yeast two-hybrid screening strain HF7c described above. HF7c was then transformed with the rat mid brain two-hybrid library. Approximately six million transformants were obtained and plated in selection medium. Colonies that grew in the selection medium and expressed the beta-galactosidase reporter gene were further characterized and subjected to retransformation and specificity assays. The retransformation and specificity tests yielded three PCIP clones (rat 1v, 8t, and 9qm) that were able to bind to the Kv4.3 polypeptide.

The full length sequences for the rat 1v gene, and partial sequences for 8t and 9q genes were derived as follows. The partial rat PCIP sequences were used to prepare probes, which were then used to screen, for example, rat mid brain cDNA libraries. Positive clones were identified, amplified and sequenced using standard techniques, to obtain the full length sequence. Additionally, a rapid amplification of the existing rat PCIP cDNA ends (using for example, 5' RACE, by Gibco, BRL) was used to complete the 5' end of the transcript.

EXAMPLE 2: IDENTIFICATION OF HUMAN 1v cDNA

To obtain the human 1v nucleic acid molecule, a cDNA library made from a human hippocampus (Clontech, Palo Alto, CA) was screened under low stringency conditions as follows: Prehybridization for 4 hours at 42°C in Clontech Express Hyb solution, followed by overnight hybridization at 42°C. The probe used was a PCR-generated fragment including nucletides 49-711 of the rat sequence labeled with ^{32}P dCTP. The filters were washed 6 times in 2XSSC/0.1% SDS at 55°C. The same conditions were used for secondary screening of the positive isolates. Clones thus obtained were sequenced using an ABI automated DNA Sequencing system, and compared to the rat sequences shown in SEQ ID NO:3 as well as to known sequences from the GenBank database. The largest clone from the library screen was subsequently subcloned into pBS-KS+ (Stratagene, La Jolla, CA) for sequence verification. The 515 base pair clone was determined to represent the human homolog of the 1v gene, encompasing 211 base pairs of 5' UTR and a 304 base pair coding region. To generate the full-length cDNA, 3' RACE was used according to the manufacturers instructions (Clontech Advantage PCR kit).

EXAMPLE 3: ISOLATION AND CHARACTERIZATION OF 1V SPLICE VARIANTS

The mouse 1v shown in SEQ ID NO:5 and the rat 1vl splice variant shown in SEQ ID NO:7 was isolated using a two-hybrid assay as described in Example 1. The mouse 1vl splice variant shown in SEQ ID NO: 7 was isolated by screening a mouse brain cDNA library, and the rat 1vn splice variant shown in SEQ ID NO:11 was isolated by BLAST searching.

EXAMPLE 4: ISOLATION AND IDENTIFICATION OF 9Q AND OTHER PCIPs

Rat 9ql (SEQ ID NO: 15) was isolated by database mining, rat 9qm (SEQ ID NO: 21) was isolated by a two-hybrid assay, and rat 9qc (SEQ ID NO:27) was identified by database mining. Human 9ql (SEQ ID NO: 13), and human 9qs (SEQ ID NO: 23) were identified as described in Example 2. Mouse 9ql (SEQ ID NO:17), monkey 9qs (SEQ ID NO:25), human p195 (SEQ ID NO:31), W28559 (SEQ ID NO:37), human p193 (SEQ ID

NO:39), rat p19 (SEQ ID NO:33), and mouse p19 (SEQ ID NO:35) were identified by database mining. Rat 8t (SEQ ID NO:29) was identified using a two-hybrid assay.

The human genomic 9q sequence (SEQ ID NOs:46 and 47) was isolated by screening a BAC genomic DNA library (Reasearch Genetics) using primers which were designed based on the sequence of the human 9qm cDNA. Two positive clones were identified (448O2 and 721I17) and sequenced.

EXAMPLE 5: EXPRESSION OF p19, 1V, 8T, AND 9Q mRNA IN RAT TISSUES

PCIP molecules, e.g., 9q and 8t, were demonstrated to be predominantly expressed in the heart. Briefly, rat or mouse multiple tissue Northern blots (Clontech) were probed with a [^{32}P]-labeled cDNA probe directed at the p19 sequence, the 5'-untranslated and 5'-coding region of the rat 1v sequence (nucleotides 35-124; SEQ ID NO:3) (this probe is specific for rat 1v and rat 1vl), the 5' coding region of the 8t sequence (nucleotides 1-88; SEQ ID NO:29) (this probe is specific for 8t), or the 5' end of the rat 9qm sequence (nucleotides 1-195; SEQ ID NO:21) (this probe is specific for all 9q isoforms, besides 8t). Blots were hybridized using standard techniques.

The results indicated that p19 is expressed predominantly in the brain, but also in the heart. Moreover, northern blots hybridized with the rat 1v probe revealed a single band at 2.3kb only in the lane containing brain RNA, suggesting that 1v expression is brain specific. Northern blots probed with the rat 8t probe revealed a major band at 2.4kb. The rat 8t band was most intense in the lane containing heart RNA and there was also a weaker band in the lane containing brain RNA. Northern blots hybridized with the 9q cDNA probe revealed a major band at 2.5kb and a minor band at over 4kb with predominant expression in heart and brain. The minor band may represent incompletely spliced or processed 9q mRNA.

EXAMPLE 6: EXPRESSION OF 1V, 8T, AND 9Q IN BRAIN

Expression of the rat 1v and 8t/9q genes in the brain was examined by *in situ hybridization* histochemistry (ISHH) using [^{35}S]-labeled cRNA probes and a hybridization procedure identical to that described in Rhodes et al. (1996) J. Neurosci., 16:4846-4860. Templates for preparing the cRNA probes were generated by standard PCR methods. Briefly, oligonucleotide primers were designed to amplify a fragment of 3'- or 5'-untranslated region of the target cDNA and in addition, add the promoter recognition sequences for T7 and T3 polymerase. Thus, to generate a 300 nucleotide probe directed at the 3'-untranslated region of the 1v mRNA, we used the following primers: 5-TAATACGACTCACTATAGGGACTGGCCATCCTGCTCTCAG-3 (T7, forward, sense; SEQ ID NO:42)

5-ATTAACCCTCACTAAAGGGACACTACTGTTTAAGCTCAAG-3 (T3, reverse, antisense; SEQ ID NO:43). The underlined bases correspond to the T7 and T3 promoter sequences. To generate a probe directed at a 325 bp region of 3'-untranslated sequence shared by the 8t and 9q mRNAs, the following primers were used:

5-TAATACGACTCACTATAGGGCACCTCCCCTCCGGCTGTTC-3 (T7, forward, sense; SEQ ID NO:44)

5-ATTAACCCTCACTAAAGGGAGAGCAGCAGCATGGCAGGGT-3 (T3, reverse, antisense; SEQ ID NO:45).

Autoradiograms of rat brain tissue sections processed for ISHH localization of 1v or 8t/9q mRNA expression revealed that 1v mRNA is expressed widely in brain in a pattern consistent with labeling of neurons as opposed to glial or endothelial cells. 1v mRNA is highly expressed in cortical, hippocampal, and striatal interneurons, the reticlar nucleus of the thalamus, the medial habenula, and in cerebellar granule cells. 1v mRNA is expressed at moderate levels in midbrain nuclei including the substantia nigra and superior colliculus, in several other thalamic nuclei, and in the medial septal and diagonal band nuclei of the basal forebrain.

Because the probe used to analyze the expression of 8t and 9q hybridizes to a region of the 3-untranslated region that is identical in the 8t and 9q mRNAs, this probe generates a composite image that reveals that 8t/9q mRNA is expressed widely in brain in a pattern that partly overlaps with that for 1v as described above. However, 8t/9q mRNA is highly expressed in the striatum, hippocampal formation, cerebellar granule cells, and neocortex. 8t/9q mRNA is expressed at moderate levels in the midbrain, thalamus, and brainstem. In may of these areas, 8t./9q mRNA appears to be concentrated in interneurons in addition to principal cells, and in all regions 8t/9q expression appears to be concentrated in neurons as apposed to glial cells.

Single- and double-label immunohistochemistry revealed that the PCIP and Kv4 polypeptides are precisely colocalized in many of the cell types and brain regions where PCIP and Kv4 mRNAs are coexpressed. For example, 9qm colocalized with Kv4.2 in the somata and dendrites of hippocampal granule and pyramidal cells, neurons in the medial habenular nucleus and in cerebellar basket cells, while 1v colocalized with Kv4.3 in layer II neurons of posterior cingulate cortex, hippocampal interneurons, and in a subset of cerebellar granule cells. Immunoprecipitation analyses indicated that 1v and 9qm are coassociated with Kv4 α-subunits in rat brain membranes.

EXAMPLE 7: CO-ASSOCIATION OF PCIPs AND Kv4 CHANNELS IN COS AND CHO CELLS

COS1 and CHO cells were transiently transfected with individual PCIPs (KChIP1, KChIP2, KChIP3) alone or together with Kv4.2 or Kv4.3 using the lipofectamine plus

procedure essentially as described by the manufacturer (Boehringer Mannheim). Forty-eight hours after the transfection, cells were washed, fixed, and processed for immunofluorescent visualization as described previously (Bekele-Arcuri et al. (1996) Neuropharmacology, 35:851-865). Affinity-purified rabbit polyclonal or mouse monoclonal antibodies to the Kv4 channel or the PCIP protein were used for immunofluorescent detection of the target proteins.

When expressed alone, the PCIPs were diffusely distributed throughout the cytoplasm of COS-1 and CHO cells, as would be expected for cytoplasmic proteins. In contrast, when expressed alone, the Kv4.2 and Kv4.3 polypeptides were concentrated within the perinuclear ER and Golgi compartments, with some immunoreactivity concentrated in the outer margins of the cell. When the PCIPs were coexpressed with Kv4 α-subunits, the characteristic diffuse PCIP distribution changed dramatically, such that the PCIPs precisely colocalized with the Kv4 α-subunits. This redistribution of the PCIPs did not occur when they were coexpressed with the Kv1.4 α-subunit, indicating that altered PCIP localization is not a consequence of overexpression and that these PCIPs associate specifically with Kv4-family α-subunits.

To verify that the PCIP and Kv4 polypeptides are tightly associated and not simply colocalized in co-transfected cells, reciprocal immunoprecipitation analyses were performed using the PCIP and channel-specific antibodies described above. All three PCIP polypeptides coassociated with Kv4 α-subunits in cotransfected cells, as evidenced by the ability of anti-Kv4.2 and anti-Kv4.3 antibodies to immunoprecipitate the KChIP1, KChIP2, and KChIP3 proteins from lysates prepared from cotransfected cells, and by the ability of anti-PCIP antibodies to immunoprecipitate Kv4.2 and Kv4.3 α-subunits from these same lysates. The cells were lysed in buffer containing detergent and protease inhibitors, and prepared for immunoprecipitation reactions essentially as described previously (Nakahira et al. (1996) J. Biol. Chem., 271:7084-7089). Immunoprecipitations were performed as described in Nakahira et al. (1996) J. Biol. Chem., 271:7084-7089 and in Harlow E. and Lane, D., Antibodies:A Laboratory Manual, Cold Spring Harbor Laboratory, c1988. The products resulting from the immunoprecipitation were size fractionated by SDS-PAGE and transferred to nitrocellulose filters using standard procedures.

To confirm that the cytoplasmic N-terminus of Kv4 channels is sufficient for the interaction with the PCIPs KChIP1 or KChIP2 were co-expressed with a Kv4.3 mutant (Kv4.3ΔC) that lacks the entire 219 amino acid cytoplasmic C-terminal tail. In transiently transfected COS-1 cells, the Kv4.3ΔC mutant was extensively trapped within the perinuclear ER and Golgi: little or no staining was observed at the outer margins of the cell. Nonetheless, KChIP1 and KChIP2 precisely colocalized with Kv4.3ΔC in cotransfected cells, and moreover, Kv4.3ΔC was efficiently coimmunoprecipitated by PCIP antibodies,

indicating that the interaction of these PCIPs with Kv4 α-subunits does not require the cytoplasmic C-terminus of the channel.

EXAMPLE 8: CO-ASSOCIATION OF PCIPs AND Kv4 CHANNELS IN NATIVE TISSUES

To determine whether PCIPs colocalize and co-associate with Kv4 subunits in native tissues, Kv4- and PCIP-specific antibodies were used for single and double-label immunohistochemical analyses and for reciprocal coimmunoprecipitation analyses of rat brain membranes. Immunohistochemical staining of rat brain sections indicated that KChIP1 and KChIP2 colocalize with Kv4.2 and Kv4.3 in a region and cell type-specific manner. For example, KChIP1 colocalized with Kv4.3 in hippocampal interneurons, cerebellar granule cells, and cerebellar glomeruli, a specialized synaptic arrangement between the dendrites of cerebellar basket and golgi cells and mossy fiber terminals. KChIP2 colocalized with Kv4.3 and Kv4.2 in the dendrites of granule cells in the dentate gyrus, in the apical and basal dendrites of hippocampal and neocortical pyramidal cells, and in several subcortical structures including the striatum and superior colliculus. Co-immunoprecipitation analyses performed using synaptic membranes prepared from whole rat brain revealed that the PCIPs (KChIPs 1, 2, and 3) are tightly associated with Kv4.2 and Kv4.3 in brain K+ channel complexes. Anti-PCIP antibodies immunoprecipitated Kv4.2 and Kv4.3 from brain membranes, and anti-Kv4.2 and Kv4.3 antibodies immunoprecipitated the PCIPs. None of the PCIP polypeptides were immunoprecipitated by anti-Kv2.1 antibodies, indicating that the association of these PCIPs with brain Kv channels may be specific for Kv4 α-subunits. Taken together, these anatomical and biochemical analyses indicate that these PCIPs are integral components of native Kv4 channel complexes.

EXAMPLE 9: PCIPs ARE CACIUM BINDING PROTEINS

To determine whether KChIPs 1, 2, and 3 bind Ca2+, GST-fusion proteins were generated for each PCIP and the ability of the GST-PCIP proteins, as well as the recombinant PCIP polypeptides enzymatically cleaved from GST, to bind $^{45}Ca2+$ was examined using a filter overlay assay (described in, for example, Kobayashi *et al.* (1993) Biochem. Biophys. Res. Commun. 189(1):511-7). All three PCIP polypeptides, but not an unrelated GST-fusion protein, display strong $^{45}Ca2+$ binding in this assay. Moreover, all three PCIP polypeptides display a Ca2+-dependent mobility shift on SDS-PAGE, indicating that like the other members of this family, KChIPs 1, 2 and 3 are in fact Ca2+-binding proteins (Kobuyashi *et al.* (1993) *supra*; Buxbaum *et al.* Nef (1996). Neuron-specific calcium sensors (the NCS-1 subfamily). In: Celio MR (ed) Guidebook to the calcium-binding proteins. Oxford University Press, New York, pp94-98; Buxbaum J.D., *et al.* (1998) *Nature Med.* 4(10):1177-81.

EXAMPLE 10: ELECTROPHYSIOLOGICAL CHARACTERIZATION OF PCIPs

Because PCIPs, e.g., KChIP1 (1v), KChIP2 (9ql), and KChIP3 (p19), colocalize and coassociate with Kv4 α-subunits in brain, another critical question was to determine whether these PCIPs alter the conductance properties of Kv4 channels. To address this issue, Kv4.2 and Kv4.3 were expressed alone and in combination with individual PCIPs.

CHO cells were transiently-transfected with cDNA using the DOTAP lipofection method as described by the manufacturer (Boehringer Mannheim, Inc.). Transfected cells were identified by cotransfecting enhanced GFP along with the genes of interest and subsequently determining if the cells contained green GFP fluorescence. Currents in CHO cells were measured using the patch-clamp technique (Hamill et al. 1981. Pfluegers Arch. 391: 85-100).

Transient transfection of the rat Kv4.2 α-subunit in CHO cells resulted in expression of a typical A-type K+ conductance. Coexpression of Kv4.2 with KChIP1 revealed several dramatic effects of KChIP1 on the channel (Figure 41 and Table 1). First, the amplitude of the Kv4.2 current increased approximately 7.5 fold in the presence of KChIP1 (amplitude of Kv4.2 alone = 0.60+/- 0.096 nA/cell; Kv4.2 + KChIP1 = 4.5 +/- 0.55 nA/cell). When converted into current density by correcting for cell capacitance, a measure of cell surface membrane area, the Kv4.2 current density increased 12 fold with coexpression of KChIP1 (Kv4.2 alone = 25.5 +/- 3.2 pA/pF; Kv4.2 + KChIP1 = 306.9 +/- 57.9 pA/pF), indicating that KChIPs promote and/or stabilize Kv4.2 surface expression. Together with this increase in current density, a dramatic leftward shift in the threshold for activation of Kv4.2 currents was observed in cells expressing Kv4.2 and KChIP1 (activation V1/2 for Kv4.2 alone = 20.8 +/- 7.0mV, Kv4.2 + KChIP1 = -12.1+/- 1.4 mV). Finally, the kinetics of Kv4.2 inactivation slowed considerably when Kv4.2 was coexpressed with KChIP1 (inactivation time constant of Kv4.2 alone = 28.2 +/- 2.6 ms; Kv4.2 + KChIP1 = 104.1 +/- 10.4 ms), while channels recovered from inactivation much more rapidly in cells expressing both Kv4.2 and KChIP1 (recovery tau = 53.6 +/- 7.6 ms) versus cells expressing Kv4.2 alone (recovery tau = 272.2 +/- 26.1 ms).

KChIPs1, 2 and 3 have distinct N-termini but share considerable amino acid identity within the C-terminal "core" domain. Despite their distinct N-termini, the effects of KChIP2 and KChIP3 on Kv4.2 current density and kinetics were strikingly similar to those produced by KChIP1 (Table1). Thus to confirm that the conserved C-terminal core domain, which contains all three EF-hands, is sufficient to modulate Kv4 current density and kinetics, N-terminal truncation mutants of KChIP1 and KChIP2 were prepared. The KChIP1ΔN2-31 and KChIP2ΔN2-67 mutants truncated KChIP1 and KChIP2, respectively, to the C-terminal 185 amino acid core sequence. Coexpression of KChIP1ΔN2-31 or KChIP2ΔN2-67 with Kv4.2 in CHO cells produced changes in Kv4.2 current density and

kinetics that were indistinguishable from the effects produced by full-length KChIP1 or KChIP2 (Table1).

To investigate whether the modulatory effects of these KChIPs are specific for Kv4 channels, KChIP1 was coexpressed with Kv1.4 and Kv2.1 in Xenopus oocytes. Xenopus oocytes were injected with 1-3 ng/oocyte of cRNA which was prepared using standard in vitro transcription techniques (Sambrook et al. 1989. Molecular Cloning: a laboratory manual, Cold Spring Harbor Press). Currents in oocytes were measured with a two-electrode voltage clamp. KChIP1 did not appear to have any effect on Kv1.4 or Kv2.1 currents (Table2), indicating that these functional effects may be specific for Kv4 channels. As a final control for the KChIP effects and to verify that the KChIPs' effects on Kv4 currents are independent of expression system, the above kinetic analyses were repeated after expressing Kv4.3 and KChIP mRNAs in Xenopus oocytes. The effects KChIP1 on for Kv4.3 in the oocyte system were strikingly similar to those on Kv4.2 in CHO cells (Table1).

Since these KChIPs bind Ca2+, another important question is to determine whether the effects of KChIP1 on Kv4.2 currents are Ca2+-dependent. This question was addressed indirectly by introducing point mutations within each of KChIP1's EF-hand domains: one mutant has point mutations in the first two EF hands (D_{199} to A, G_{104} to A, D_{135} to A, and G_{140} to A) and the other one has point muations in all three EF hands (D_{199} to A, G_{104} to A, D_{135} to A, G_{140} to A, D_{183} to A, and G_{188} to A). These mutations substituted alanine for the two most highly conserved amino acids within the EF-hand consensus (Figure 25; Linse, S. and Forsen, S. (1995) Determinants that govern high-affinity Calcium binding. In Means, S. (Ed.)Advances in second messenger and phosphoprotein research. New York, Ravens Press,. 30:89-150). Coexpression of this KChIP1 triple EF-hand mutant with Kv4.2 or Kv4.3 in COS cells indicated that this mutant colocalizes and is efficiently coimmunoprecipitated with Kv4 α-subunits in COS-1 cells. However, these EF-hand point mutations completely eliminated the effects of KChIP1 on Kv4.2 kinetics (Table1). Taken together, these results indicate that the binding interaction between KChIP1 and Kv4.2 is Ca2+ independent, while modulation of Kv4.2 kinetics by KChIP1 is either Ca2+-dependent or sensitive to structural changes induced by point mutations within the EF-hand domains.

TABLE 1

Functional effect of KchIPs on Kv4 channels

Current Parameter	rKv4.2 + vector	rKv4.2 + KchIP1	rKv4.2 + KchIP1 ΔN2-31	rKv4.2 + KchIP2	rKv4.2 + KchIP2 ΔN2-67	rKv4.2 + KchIP3	rKv4.3	rKv4.3 + KchIP1
Peak Current	0.60*	4.5*	6.0*	3.3*	5.8*	3.5*	7.7μA	18.1μA*

(nA/cell at 50 MV)	±0.096	±0.055	±1.1	±0.45	±1.1	±0.99	±2.6	±3.8
Peak Current Density	25.5	306.9*	407.2*	196.6*	202.6*	161.7*	---	---
(pA/pF at 50 mV)	±3.2	±57.9	±104.8	±26.6	±27.5	±21.8		
Inactivation time constant	28.2	104.1	129.2	95.1*	109.5*	67.2*	56.3	135.0
(ms, at 50 mV)	±2.6	±10.4	±14.2	±8.3	±9.6	±14.1	±6.6	±15.1
Recovery from Inactivation Time constant	272.2	53.6*	98.1*	49.5*	36.1*	126.1*	327.0	34.5*

* Significantly different from control.

TABLE 2

Functional effects of KChIPs on other Kv channels

	Oocytes		Oocytes	
Current Parameter	HKv1.4	hKv1.4 + 1v	HKv2.1	HKv2.1 + 1v
Peak Current	8.3	6.5	3.7	2.9
(μA/cell at 50 MV)	± 2.0	± 0.64	± 0.48	± 0.37
Inactivation time constant	53.2	58.2	1.9 s	1.7 s
(ms, at 50 mV)	± 2.8	± 6.6	± 0.079	0.078

Recovery from Inactivation time constant (sec, at –80 mV)	1.9	1.6	7.6	7.7
Activation $V_{1/2}$ (mV)	-21.0	-20.9	12.0	12.4
Steady-state Inactivation V1/2 (mV)	-48.1	-47.5	-25.3	-23.9

EXAMPLE 11: EFFECTS OF KChIP1 AND KChIP2 ON SURFACE EXPRESSION OF KV4-α SUBUNITS IN COS-1 CELLS

To examine the ability of KChIP1 to enhance the surface expression of Kv4 channels, the ability of KChIP1 to promote the formation of surface co-clusters of Kv4 channels and PSD-95 was monitored. PSD-95 is used to facilitate the visualization of the complex.

To facilitate the interaction between Kv4.3 and PSD-95, a chimeric Kv4.3 subunit (Kv4.3ch) was generated in which the C-terminal 10 amino acids from rKv1.4 (SNAKAVETDV, SEQ ID NO:73) were appended to the C-terminus of Kv4.3. The C-terminal 10 amino acids from rKv1.4 were used because they associate with PSD-95 and confer the ability to associate with PSD-95 to the Kv4.3 protein when fused to the Kv4.3 C-terminus. Expression of Kv4.3ch in COS-1 cells revealed that the Kv4.3ch polypeptide was trapped in the perinuclear cytoplasm, with minimal detectable Kv4.3ch immunoreactivity at the outer margins of the cell. When Kv4.3ch was co-expressed with PSD-95, PSD-95 became trapped in the perinuclear cytoplasm and co-localized with Kv4.3ch. However, when KChIP1 was co-expressed with Kv4.3ch and PSD-95, large plaque-like surface co-clusters of Kv4.3ch, KChIP1 and PSD-95 were observed. Triple-label immunofluorescence confirmed that these surface clusters contain all three polypeptides, and reciprocal co-immunoprecipitation analyses indicated that the three polypeptides are co-associated in these surface clusters. Control experiments indicated that KChIP1 does not interact with PSD-95 alone, and does not co-localize with Kv1.4 and PSD-95 in surface clusters. Taken together, these data indicate that KChIP1 may promote the transit of the Kv4.3 subunits to the cell surface.

EXAMPLE 12: CHARACTERIZATION OF THE PCIP PROTEINS

In this example, the amino acid sequences of the PCIP proteins were compared to amino acid sequences of known proteins and various motifs were identified.

The 1v polypeptide, the amino acid sequence of which is shown in SEQ ID NO:3 is a novel polypeptide which includes 216 amino acid residues. Domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York), were identified by sequence alignment (see Figure 21).

The 8t polypeptide, the amino acid sequence of which is shown in SEQ ID NO:30 is a novel polypeptide which includes 225 amino acid residues. Calcium binding domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York), were identified by sequence alignment (see Figure 21).

The 9q polypeptide is a novel polypeptide which includes calcium binding domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York (see Figure 21).

The p19 polypeptide is a novel polypeptide which includes calcium binding domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York (see Figure 21).

A BLASTN 2.0.7 search (Altschul et al. (1990) *J. Mol. Biol.* 215:403) of the nucleotide sequence of rat 1vl revealed that the rat 1vl is similar to the rat cDNA clone RMUAH89 (Accession Number AA849706). The rat 1 vl nucleic acid molecule is 98% identical to the rat cDNA clone RMUAH89 (Accession Number AA849706) over nucleotides 1063 to1488.

A BLASTN 2.0.7 search (Altschul et al. (1990) *J. Mol. Biol.* 215:403) of the nucleotide sequence of human 9ql revealed that the human 9ql is similar to the human cDNA clone 1309405 (Accession Number AA757119). The human 9 ql nucleic acid molecule is 98% identical to the human cDNA clone 1309405 (Accession Number AA757119) over nucleotides 937 to1405.

A BLASTN 2.0.7 search (Altschul et al. (1990) *J. Mol. Biol.* 215:403) of the nucleotide sequence of mouse P19 revealed that the mouse P19 is similar to the Mus musculus cDNA clone MNCb-7005 (Accession Number AU035979). The mouse P19 nucleic acid molecule is 98% identical to the Mus musculus cDNA clone MNCb-7005 (Accession Number AU035979) over nucleotides 1 to 583.

EXAMPLE 13: EXPRESSION OF RECOMBINANT PCIP PROTEINS IN BACTERIAL CELLS

In this example, PCIP is expressed as a recombinant glutathione-S-transferase (GST) fusion polypeptide in *E. coli* and the fusion polypeptide is isolated and characterized.

Specifically, PCIP is fused to GST and this fusion polypeptide is expressed in *E. coli*, e.g., strain BI21. Expression of the GST-PCIP fusion protein in BI21 is induced with IPTG. The recombinant fusion polypeptide is purified from crude bacterial lysates of the induced BI21 strain by affinity chromatography on glutathione beads. Using polyacrylamide gel electrophoretic analysis of the polypeptide purified from the bacterial lysates, the molecular weight of the resultant fusion polypeptide is determined.

Rat 1v and 9ql were cloned into pGEX-6p-2 (Pharmacia). The resulting recombinant fusion proteins were expressed in E. coli cells and purified following art known methods (described in, for example, *Current Protocols in Molecular Biology*, eds. Ausubel et al. John Wiley & Sons: 1992). The identities of the purified proteins were verified by western blot analysis using antibodies raised against peptide epitopes of rat 1v and 9ql.

EXAMPLE 14: EXPRESSION OF RECOMBINANT PCIP PROTEINS IN COS CELLS

To express the PCIP gene in COS cells, the pcDNA/Amp vector by Invitrogen Corporation (San Diego, CA) is used. This vector contains an SV40 origin of replication, an ampicillin resistance gene, an *E. coli* replication origin, a CMV promoter followed by a polylinker region, and an SV40 intron and polyadenylation site. A DNA fragment encoding the entire PCIP protein and an HA tag (Wilson et al. (1984) *Cell* 37:767) or a FLAG tag fused in-frame to its 3' end of the fragment is cloned into the polylinker region of the vector, thereby placing the expression of the recombinant protein under the control of the CMV promoter.

To construct the plasmid, the PCIP DNA sequence is amplified by PCR using two primers. The 5' primer contains the restriction site of interest followed by approximately twenty nucleotides of the PCIP coding sequence starting from the initiation codon; the 3' end sequence contains complementary sequences to the other restriction site of interest, a translation stop codon, the HA tag or FLAG tag and the last 20 nucleotides of the PCIP coding sequence. The PCR amplified fragment and the pCDNA/Amp vector are digested with the appropriate restriction enzymes and the vector is dephosphorylated using the CIAP enzyme (New England Biolabs, Beverly, MA). Preferably the two restriction sites chosen are different so that the PCIP gene is inserted in the correct orientation. The ligation mixture is transformed into *E. coli* cells (strains HB101, DH5a, SURE, available from Stratagene Cloning Systems, La Jolla, CA, can be used), the transformed culture is plated on ampicillin media plates, and resistant colonies are selected. Plasmid DNA is isolated from transformants and examined by restriction analysis for the presence of the correct fragment.

COS cells are subsequently transfected with the PCIP-pcDNA/Amp plasmid DNA using the calcium phosphate or calcium chloride co-precipitation methods, DEAE-dextran-mediated transfection, lipofection, or electroporation. Other suitable methods for

transfecting host cells can be found in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989. The expression of the PCIP polypeptide is detected by radiolabelling (^{35}S-methionine or ^{35}S-cysteine available from NEN, Boston, MA, can be used) and immunoprecipitation (Harlow, E. and Lane, D. *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1988) using an HA specific monoclonal antibody. Briefly, the cells are labelled for 8 hours with ^{35}S-methionine (or ^{35}S-cysteine). The culture media are then collected and the cells are lysed using detergents (RIPA buffer, 150 mM NaCl, 1% NP-40, 0.1% SDS, 0.5% DOC, 50 mM Tris, pH 7.5). Both the cell lysate and the culture media are precipitated with an HA specific monoclonal antibody. Precipitated polypeptides are then analyzed by SDS-PAGE.

Alternatively, DNA containing the PCIP coding sequence is cloned directly into the polylinker of the pCDNA/Amp vector using the appropriate restriction sites. The resulting plasmid is transfected into COS cells in the manner described above, and the expression of the PCIP polypeptide is detected by radiolabelling and immunoprecipitation using a PCIP specific monoclonal antibody.

Rat 1v was cloned into the mammalian expresssion vector pRBG4. Transfections into COS cells were performed using LipofectAmine Plus (Gibco BRL) following the manufacturer's instructions. The expressed 1v protein was detected by immunocytochemistry and/or western blot analysis using antibodies raised against 1v in rabbits or mice.

EXAMPLE 15: IDENTIFICATION AND CHARACTERIZATION OF HUMAN FULL LENGTH P19

The human full length p19 sequence was identified using RACE PCR. The sequence of p19 (also referred to as KChIP3) is shown in Figure 16. The amino acid sequence of human p19 is 92% identical to the mouse p19 gene (SEQ ID NO:35).

TBLASTN searches using the protein sequence of human p19 revealed that human p19 is homologous to two sequences, Calsenilin (described in (1998) *Nature Medicine* 4: 1177-1181) and DREAM, a Ca2+-dependent regulator of prodynorphin and c-fos transcription (described in Carrion *et al.* (1999) *Nature* 398: 80-84). Human p19 is 100% identical at the nucleotide level to Calsenilin (but extends 3' to the published sequence) and 99% identical at the nucleotide level to DREAM.

The ability of p19 (as well as other PCIP family members) to co-localize with presenilin and act as transcription factors is determined using art known techniques such as northern blots, *in situ* hybridization, β-gal assays, DNA mobility assays (described in, for

example, Carrion *et al.* (1999) *Nature* 398:80) and DNA mobility supershift assays, using antibodies specific for KchIPs.

Other assays suitable for evaluating the association of PCIP family members with presenilins is co-immunoprecipitation (described in, for example, Buxbaum *et al.* (1998) *Nature Medicine* 4:1177).

EXAMPLE 16: IDENTIFICATION AND CHARACTERIZATION OF MONKEY KChIP4

In this example, the identification and characterization of the genes encoding monkey KChIP4a (jlkbd352e01t1) and alternatively spliced monkey KChIP4b (jlkbb231c04t1), KChIP4c (jlkxa053c02), and KChIP4d (jlkx015b10) is described. TBLASTN searches in proprietary databases with the sequence of the known PCIP family members, lead to the identification of four clones jlkbb231c04t1, jlkbd352e01t1, jlkxa053c02, and jlkx015b10. The four monkey clones were obtained and sequenced.

The sequences of proprietary monkey clones jlkbb231c04t1 and jlkbd352e01t1 were found to correspond to alternately spliced variants of an additional PCIP family member, referred to herein as KChIP4. Clone jlkbb231c04t1 contains a 822bp deletion relative to jlkbd352e01t1 (presumably due to splicing out of an exon), resulting in the loss of the final EF hand domain. In clone jlkbd352e01t1, the final EF hand domain is preserved, and the C-terminus is highly homologous to that of PCIP family members 1v, 9ql, and p19. Overall identity in the homologous C-termini among KChIP4, 1v, 9ql, and p19 ranged from 71%-80% at the amino acid level (alignments were performed using the CLUSTALW).

Monkey KChIP4c and KChIP4d were discovered by BLASTN search using monkey KChIP4a as a query for searching a proprietary database.

The nucleotide sequence of the monkey KChIP4a cDNA and the predicted amino acid sequence of the KChIP4a polypeptide are shown in Figure 23 and in SEQ ID NOs:48 and 49, respectively.

The nucleotide sequence of the monkey KChIP4b cDNA and the predicted amino acid sequence of the KChIP4b polypeptide are shown in Figure 24 and in SEQ ID NOs:50 and 51, respectively.

The nucleotide sequence of the monkey KChIP4c cDNA and the predicted amino acid sequence of the KChIP4c polypeptide are shown in Figure 35 and in SEQ ID NOs:69 and 70, respectively.

The nucleotide sequence of the monkey KChIP4d cDNA and the predicted amino acid sequence of the KChIP4d polypeptide are shown in Figure 36 and in SEQ ID NOs:71 and 72, respectively.

Figure 37 depicts an alignment of the protein sequences of KChIP4a, KChIP4b, KChIP4c, and KChIP4d.

Rat KChIP4 is predominantly expressed in the brain, and weakly in the kidney, but not in the heart, brain, spleen, lung, liver, skeletal muscle or testes, as indicated by northern blot experiments in which a northern blot purchased from Clontech was probed with a DNA fragment from the 3'-untranslated region of rat KChIP4.

EXAMPLE 17: IDENTIFICATION AND CHARACTERIZATION OF HUMAN AND RAT 33b07

In this example, the identification and characterization of the genes encoding rat and human 33b07 is described. Partial rat 33b07 (clone name 9o) was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as bait. The full length rat 33b07 clone was identified by mining of proprietary databases.

The nucleotide sequence of the full length rat 33b07 cDNA and the predicted amino acid sequence of the rat 33b07 polypeptide are shown in Figure 26 and in SEQ ID NOs:52 and 53, respectively. The rat 33b07 cDNA encodes a protein having a molecular weight of approximately 44.7 kD and which is 407 amino acid residues in length.

Rat 33b07 binds rKv4.3N and rKv4.2N with slight preference for rKv4.2N in yeast 2-hybrid assays. In contrast, rat 33b07 does not bind rKv1.1N, indicating that the rat 33b07-Kv4N interaction is specific.

Rat 33b07 is expressed predominantly in the brain as determined by northern blot analysis.

The human 33b07 ortholog (clone 106d5) was also identified by mining of proprietary databases. The nucleotide sequence of the full length human 33b07 cDNA and the predicted amino acid sequence of the human 33b07 polypeptide are shown in Figure 27 and in SEQ ID NOs:54 and 55, respectively. The human 33b07 cDNA encodes a protein having a molecular weight of approximately 45.1 kD and which is 414 amino acid residues in length.

Human 33b07 is 99% identical to the human KIAA0721 protein (GenBank Accession Number: AB018264) at the amino acid level. However, GenBank Accession Number: AB018264 does not have a functional annotation. Human 33b07 is also homologous to Testes-specific (Y-encoded) proteins (TSP(Y)s), SET, and Nucleosome Assembly Proteins (NAPs). The human 33b07 is 38% identical to human SET protein (GenBank Accession Number Q01105=U51924) over amino acids 204 to 337 and 46% identical over amino acids 334 to 387.

Human SET is also called HLA-DR associated protein II (PHAPII) (Hoppe-Seyler (1994) *Biol. Chem.* 375:113-126) and in some cases is associated with acute undifferentiated leukemia (AUL) as a result of a translocation event resulting in the formation of a SET-CAN fusion gene (Von Lindern M. *et al.* (1992) *Mol. Cell. Biol.* 12:3346-3355). An alternative spliced form of SET is also called Template Activating Factor-I alpha (TAF). TAF is found

to be associated with myeloid leukemogenesis (Nagata K. *et al.* (1995) *Proc. Natl. Acad. Sci. U.S.A.* 92 (10), 4279-4283). Human SET is also a potent protein inhibitor of phosphatase 2A (Adachi Y. *et al.* (1994) *J. Biol. Chem.* 269:2258-2262). NAPs may be involved in modulating chromatin formation and contribute to regulation of cell proliferation (Simon H.U. *et al.* (1994) *Biochem. J.* 297, 389-397).

Thus, due to its homology to the above identified proteins, 33b07 may function as a protein inhibitor of phosphatase, an oncogene, and/or a chromatin modulator. The homology of 33b07 to SET, a protein phosphatase inhibitor, is of particular interest. Many channels, in particular the Kv4 channels (with which 33b07 is associated), are known to be regulated by phosphorylation by PKC and PKA ((1998) *J. Neuroscience* 18(10): 3521-3528; Am J Physiol 273: H1775-86 (1997)). Thus, 33b07 may modulate Kv4 activity by regulating the phosphorylation status of the potassium channel.

EXAMPLE 18: IDENTIFICATION AND CHARACTERIZATION OF RAT 1p

In this example, the identification and characterization of the gene encoding rat 1p is described. Partial rat 1p was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait.

The nucleotide sequence of the partial length rat 1p cDNA and the predicted amino acid sequence of the rat 1p polypeptide are shown in Figure 28 and in SEQ ID NOs:56 and 57, respectively. The rat 1p cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 267 amino acid residues in length.

Rat 1p binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays. In contrast, 1p does not bind rKv1.1N, indicating that the 1p-Kv4N interaction is specific.

Rat 1p is predominantly expressed in the brain as determined by northern blot analysis.

A BLASTP 1.4 search, using a score of 100 and a word length of 3 (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the amino acid sequences of rat 1p revealed that rat 1p is similar to the human Restin (GenBank Accession Number P30622; also named cytoplasmic linker protein-170 alpha-2 (CLIP-170), M97501)). The rat 1p protein is 58% identical to the human Restin over amino acid residues 105 to182, 55% identical to the human Restin over amino acid residues 115 to 186, 22% identical to the human Restin over amino acid residues 173 to 246, 22% identical to the human Restin over amino acid residues 169 to 218, and 58% identical to the human Restin over amino acid residues 217 to 228.

Restin is also named Reed-Sternberg intermediate filament associated protein. Reed-Sternberg cells are the tumoral cells diagnostic for Hodgkin's disease. It is suggested that Restin overexpression may be a contributing factor in the progression of Hodgkin's disease

(Bilbe G. *et al.* (1992) *EMBO J.* 11: 2103-13) and Restin appears to be an intermediate filament associated protein that links endocytic vesicles to microtubules (Pierre P, *et al.* (1992) *Cell* 70 (6), 887-900).

The cytoskeleton regulates the activity of potassium channels (see, for example, Honore E, et al. (1992) *EMBO J.* 11:2465-2471 and Levin G, et al. (1996) *J. Biol. Chem.* 271:29321-29328), as well as the activity of other channels, e.g., Ca^{++} channels (Johnson B.D. *et al.* (1993) *Neuron* 10:797-804); or Na^{+} channels (Fukuda J. *et al.* (1981) *Nature* 294:82-85).

Accordingly, based on its homology to the Restin protein, the rat 1p protein may be associated with the cytoskeleton and may modulate the activity of potassium channels, e.g., Kv4, via its association to the cytoskeleton.

EXAMPLE 19: IDENTIFICATION AND CHARACTERIZATION OF RAT 7s

In this example, the identification and characterization of the gene encoding rat 7s is described. Partial rat 7s was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Rat 7s is the rat ortholog of the human vacuolar H(+)-ATPase catalytic subunit A (Accession Number P38606 and B46091) described in, for example, van Hille B. *et al.* (1993) *J. Biol. Chem.* 268 (10), 7075-7080.

The nucleotide sequence of the partial length rat 7s cDNA and the predicted amino acid sequence of the rat 7s polypeptide are shown in Figure 29 and in SEQ ID NOs:58 and 59, respectively. The rat 7s cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 270 amino acid residues in length.

Rat 7s binds rKv4.3N and rKv4.2N with preference for rKv4.3N in yeast two-hybrid assays. In contrast, 7s does not bind rKv1.1N, indicating that the 7s-Kv4N interaction is specific.

Rat 7s is expressed at significantly higher levels in the brain and the kidney than in the lung, liver, heart, testes, and skeletal muscle, as determined by northern blot analysis.

EXAMPLE 20: IDENTIFICATION AND CHARACTERIZATION OF RAT 29x AND 25r

In this example, the identification and characterization of the gene encoding rat 29x is described. Rat 29x was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Rat 25r is a splice variant of 29x. They differ in the 5' untranslated region, but are identical in the coding region and at the amino acid level.

The nucleotide sequence of the rat 29x cDNA and the predicted amino acid sequence of the rat 29x polypeptide are shown in Figure 30 and in SEQ ID NOs:60 and 61,

respectively. The rat 29x cDNA encodes a protein having a molecular weight of approximately 40.4 kD and which is 351 amino acid residues in length.

The nucleotide sequence of the rat 25r cDNA is shown in Figure 31 and in SEQ ID NO:62. The rat 25r cDNA encodes a protein having a molecular weight of approximately 40.4 kD and which is 351 amino acid residues in length.

Rat 29x is expressed in the spleen, lung, kidney, heart, brain, testes, skeletal muscle and liver, with the highest level of expression being in the spleen and the lowest being in the liver.

Rat 29x binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays. In contrast, 29x does not bind rKv1.1N, indicating that the 29x-Kv4N interaction is specific.

Rat 29x is identical at the amino acid level to rat SOCS-1 (Suppressor Of Cytokine Signaling) described in Starr R. *et al.* (1997) *Nature* 387: 917-921; to JAB described in Endo T.A. *et al.* (1997) *Nature* 387: 921-924; and to SSI-1 (STAT-induced STAT inhibitor-1) described in Naka T. *et al.* (1997) *Nature* 387:924-928. These proteins are characterized in that they have an SH2 domain, bind to and inhibit JAK kinase, and, as a result, regulate cytokine signaling. Rat 29x contains an SH2 domain at amino acid residues 219-308 of SEQ ID NO:61.

Tyrosine phosphorylation regulates potassium channel activity (Prevarskaya N.B. *et al.* (1995) *J. Biol. Chem.* 270:24292-24299). JAK kinase phoshorylates proteins at tyrosines and is implicated in the regulation of channel activity (Prevarskaya N.B. *et al. supra*). Accordingly, based on its homology to SOCS-1, JAB, and SSI-1, rat 29x may modulate the activity of potassium channels, e.g., Kv4, by modulating JAK kinase activity.

EXAMPLE 21: IDENTIFICATION AND CHARACTERIZATION OF RAT 5p

In this example, the identification and characterization of the gene encoding rat 5p is described. Rat 5p was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait.

The nucleotide sequence of the rat 5pc DNA and the predicted amino acid sequence of the rat 5p polypeptide are shown in Figure 32 and in SEQ ID NOs:63 and 64, respectively. The rat 5p cDNA encodes a protein having a molecular weight of approximately 11.1 kD and which is 95 amino acid residues in length.

Rat 5p binds rKv4.3N and rKv4.2N with similar strength in yeast two-hybrid assays. In contrast, 5p does not bind rKv1.1N, indicating that the 5p-Kv4N interaction is specific.

Rat 5p is expressed in the spleen, lung, skeletal muscle, heart, kidney, brain, liver, and testes, as determined by northern blot analysis.

The rat 5p is identical to rat Calpactin I light chain or P10 (Accession Number P05943). P10 binds and induces the dimerization of annexin II (p36). P10 may function as a regulator of protein phosphorylation in that the p36 monomer is the preferred target of a tyrosine-specific kinase (Masiakowski P. *et al.* (1998) *Proc. Natl. Acad. Sci. U.S.A.* 85 (4): 1277-1281).

Tyrosine phosphorylation regulates the activity of potassium channels (Prevarskaya N.B. *et al. supra*). Thus, due to its identity to P10, rat 5p may modulate the activity of potassium channels, e.g., Kv4, by modulating the activity of a tyrosine-specific kinase.

EXAMPLE 22: IDENTIFICATION AND CHARACTERIZATION OF RAT 7q

In this example, the identification and characterization of the gene encoding rat 7q is described. Rat 7q was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Full length rat 7q was obtained by RACE PCR.

The nucleotide sequence of the rat 7q cDNA and the predicted amino acid sequence of the rat 7q polypeptide are shown in Figure 33 and in SEQ ID NOs:65 and 66, respectively. The rat 7q cDNA encodes a protein having a molecular weight of approximately 23.5 kD and which is 212 amino acid residues in length.

Rat 7q binds rKv4.3N and rKv4.2N with same strength in yeast two-hybrid assays. In contrast, 7q does not bind rKv1.1N, indicating that the 7q-Kv4N interaction is specific.

Rat 7q is expressed in the heart, brain, spleen, lung, liver, skeletal muscle, kidney, and testes, as determined by northern blot analysis.

Rat 7q is identical to RAB2 (rat RAS-related protein, Accession Number P05712) at the amino acid level. RAB2 appears to be involved in vesicular traffic and protein transport (Touchot N. *et al.* (1987) *Proc. Natl. Acad. Sci. U.S.A.* 84 (23): 8210-8214). Accordingly, based on its homology to RAB2, rat 7q may be involved in potassium channel, e.g., Kv4, trafficking.

EXAMPLE 23: IDENTIFICATION AND CHARACTERIZATION OF RAT 19r

In this example, the identification and characterization of the gene encoding rat 19r is described. Partial rat 19r was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Full length rat 19r was obtained by RACE PCR.

The nucleotide sequence of the rat 19r cDNA and the predicted amino acid sequence of the rat 19r polypeptide are shown in Figure 34 and in SEQ ID NOs:67 and 68,

respectively. The rat 19r cDNA encodes a protein having a molecular weight of approximately 31.9 kD and which is 271 amino acid residues in length.

Rat 19r is expressed in the heart, brain, spleen, lung, liver, skeletal muscle, kidney, and testes, as determined by northern blot analysis.

Rat 19r binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays. In contrast, 19r does not bind rKv1.1N, indicating that the 19r-Kv4N interaction is specific.

Rat 19r is identical to Rat phosphatidylinositol (PTDINS) transfer protein alpha (PTDINSTP, Accession Number M25758 or P16446) described in Dickeson S.K. *et al.* (1989) *J. Biol. Chem.* 264:16557-16564. PTDINSTP is believed to be involved in phospholipase C-beta (PLC-beta) signaling, phosphatidylinositol transfer protein (PtdIns-TP) synthesis, secrettory vesicle formation, and enhancement of phosphatidylinositol 3-kinase (PtdIns 3-kinase) activity (Cunningham E. *et al.* (1995) *Curr. Biol.* 5 (7): 775-783; (1995) *Nature* 377 (6549): 544-547; and Panaretou C. *et al.* (1997) *J. Biol. Chem.* 272 (4): 2477-2485).

Accordingly, based on its homology with PTDINSTP, rat 19r may modulate potassium channel, e.g., Kv4, activity via the PLC-beta signaling pathway and/or the PtdIns 3-kinase signaling pathway. Rat p19r may also be involved in potassium channel, e.g., Kv4, trafficking.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. A method for identifying a compound suitable for treating a cardiovascular disorder comprising:

a) contacting a PCIP polypeptide or a fragment thereof, or a cell expressing a PCIP polypeptide or a fragment thereof, with a test compound; and

b) determining whether said PCIP polypeptide or fragment thereof, binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.

2. The method of claim 1, wherein the binding of said test compound to said PCIP polypeptide or fragment thereof, is detected by a method selected from the group consisting of:

a) detection of binding by direct detection of test compound/polypeptide binding;

b) detection of binding using a competition binding assay; and

c) detection of binding using an assay for PCIP activity.

3. A method for identifying a compound suitable for treating a cardiovascular disorder, comprising:

a) incubating a cell expressing i) a potassium channel comprising a Kv4.3 or Kv4.2 subunit, or a fragment of a potassium channel comprising a Kv4.3 or Kv4.2 subunit, and ii) a PCIP polypeptide or a fragment thereof, in the presence and absence of a candidate compound; and

b) determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with said PCIP polypeptide or fragment thereof, thereby identifying a compound suitable for treating a cardiovascular disorder.

4. A method for treating a cardiovascular disorder comprising contacting a potassium channel with an effective amount of a compound that modulates the binding of a PCIP protein to said potassium channel.

5. A method for determining if a subject is at risk for a cardiovascular disorder comprising detecting, in a sample of cells from the subject an alteration in a PCIP gene which causes a mutated PCIP polypeptide to be produced.

6. A method for determining if a subject is at risk for a cardiovascular disorder comprising detecting, in a sample of cells from the subject an alteration in a PCIP gene which causes abnormal expression of a PCIP polypeptide.

7. A method for determining if a subject is at risk for a cardiovascular disorder comprising detecting, in a sample of cells from the subject an alteration in a PCIP gene which causes abnormal processing of a PCIP polypeptide.

8. A method for identifying a subject suffering from a cardiovascular disorder comprising detecting, in a sample of cells from the subject an alteration in a PCIP gene which causes a mutated PCIP polypeptide to be produced.

9. A method for identifying a subject suffering from a cardiovascular disorder comprising detecting, in a sample of cells from the subject an alteration in a PCIP gene which causes abnormal expression of a PCIP polypeptide.

10. A method for identifying a subject suffering from a cardiovascular disorder comprising detecting, in a sample of cells from the subject an alteration in a PCIP gene which causes abnormal processing of a PCIP polypeptide.

11. The method of any one of claims 1, 3, 4, 5, 6, 7, 8, 9, or 10, wherein said cardiovascular disorder is associated with an abnormal I_{to} current.

12. The method of any one of claims 1, 3, 4, 5, 6, 7, 8, 9, or 10, wherein said PCIP is 9q.

13. The method of any one of claims 1, 3, 4, 5, 6, 7, 8, 9, or 10, wherein said PCIP is 8t.

14. The method of any one of claims 1, 3, 4, 5, 6, 7, 8, 9, or 10, wherein said PCIP is p19.

15. The method of any one of claims 1, 3, 4, 5, 6, 7, 8, 9, or 10, wherein said cardiovascular disorder is long-QT syndrome.

16. The method of any one of claims 1, 3, 4, 5, 6, 7, 8, 9, or 10, wherein said cardiovascular disorder is congestive heart failure.

METHODS FOR TREATING CARDIOVASCULAR DISORDERS

Abstract of the Disclosure

The invention provides methods for identifying compounds suitable for treating a cardiovascular disorder, as well as methods for treating a cardiovascular disorder. The invention also provides methods for determining if a subject is at risk for a cardiovascular disorder.

HUMAN 1V DNA (CD:225-87:

GAATAGCCCCCTTTCACTTCTGAGTCCCTGCATGTGCGGGGCTGAAGAAGGAAGCCAGAAGCCTCCTAGCCTCGCCTCCA
CGTTTGCTGAATACCAAGCTGCAGGCGAGCTGCCGGGCGCTTTTCTCTCCTCCAATTCAGAGTAGACAAACCACGGGGAT
TTCTTTCCAGGGTAGGGGAGGGGCCGGGCCCGGGGTCCCAACTCGCACTCAAGTCTTCGCTGCCATGGGGGCCGTCATGG
GCACCTTCTCATCTCTGCAAACCAAACAAAGGCGACCCTCGAAAGATAAGATTGAAGATGAGCTGGAGATGACCATGGTT
TGCCATCGGCCCGAGGGACTGGAGCAGCTCGAGGCCCAGACCAACTTCACCAAGAGGGAGCTGCAGGTCCTTTATCGAGG
CTTCAAAAATGAGTGCCCCAGTGGTGTGGTCAACGAAGACACATTCAAGCAGATCTATGCTCAGTTTTTCCCTCATGGAG
ATGCCAGCACGTATGCCCATTACCTCTTCAATGCCTTCGACACCACTCAGACAGGCTCCGTGAAGTTCGAGGACTTTGTA
ACCGCTCTGTCGATTTTATTGAGAGGAACTGTCCACGAGAAACTAAGGTGGACATTTAATTTGTATGACATCAACAAGGA
CGGATACATAAACAAAGAGGAGATGATGGACATTGTCAAAGCCATCTATGACATGATGGGAAATACACATATCCTGTGC
TCAAAGAGGACACTCCAAGGCAGCATGTGGACGTCTTCTTCCAGAAAATGGACAAAAATAAAGATGGCATCGTAACTTTA
GATGAATTTCTTGAATCATGTCAGGAGGACGACAACATCATGAGGTCTCTCCAGCTGTTTCAAAATGTCATGTAACTGGT
GACACTCAGCCATTCAGCTCTCAGAGACATTGTACTAAACAACCACCTTAACACCCTGATCTGCCCTTGTTCTGATTTTA
CACACCAACTCTTGGGACAGAAACACCTTTTACACTTTGGAAGAATTCTCTGCTGAAGACTTTCTTATGGAACCCAGCAT
CATGTGGCTCAGTCTCTGATTGCCAACTCTTCCTCTTTCTTCTTCTTGAGAGAGACAAGATGAAATTTGAGTTTGTTTTG
GAAGCATGCTCATCTCCTCACACTGCTGCCCTATGGAAGGTCCCTCTGCTTAAGCTTAAACAGTAGTGCACAAAATATGC
TGCTTACGTGCCCCCAGCCCACTGCCTCCAAGTCAGGCAGACCTTGGTGAATCTGGAAGCAAGAGGACCTGAGCCAGATG
CACACCATCTCTGATGGCCTCCCAAACCAATGTGCCTGTTTCTCTTCCTTTGGTGGGAAGAATGAGAGTTATCCAGAACA
ATTAGGATCTGTCATGACCAGATTGGGAGAGCCAGCACCTAACATATGTGGGATAGGACTGAATTATTAAGCATGACATT
GTCTGATGACCCAAACTGCCCCG

HUMAN 1V PROTEIN

MGAVMGTFSSLQTKQRRPSKDKIEDELEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNECPSGVVNEDTFKQIYAQ

FFPHGDASTYAHYLFNAFDTTQTGSVKFEDFVTALSILLRGTVHEKLRWTFNLYDINKDGYINKEEMMDIVKAIYDMMGK

YTYPVLKEDTPRQHVDVFFQKMDKNKDGIVTLDEFLESCQEDDNIMRSLQLFQNVM

FIGURE 1

RAT 1vN (r1vN) DNA (CD: 339-1037)

GGCACACAACCCCTGGATTCTTCGGAGAATATGCCGTGAGGTGTTGCCAATTATTAGTTCTCTTGGCTAGCAGATGTTTA

GGGACTGGTtaaGCCTTTGGAGAAATTACCTTAGGAAAACGGGGAAATAAAAGCAAAGATTACCATGAATTGCAAGATTA

CCTAGCAATTGCAAGGtagGAGGAGAGAGGTGGAGGGCGGAGTAGACAGGAGGGAGGGAGAAAGtgaGAGGAAGCTAGGC

TGGTGGAAATAACCCTGCACTTGGAACAGCGGCAAAGAAGCGCGATTTTCCAGCTTtaaATGCCTGCCCGCGTTCTGCTT

GCCTACCCGGGAACGGAGATGTTGACCCAGGGCGAGTCTGAAGGGCTCCAGACCTTGGGGATAGTAGTGGTCCTGTGTTC

CTCTCTGAAACTACTGCACTACCTCGGGCTGATTGACTTGTCGGATGACAAGATCGAGGATGATCTGGAGATGACCATGG

TTTGCCATCGGCCTGAGGGACTGGAGCAGCTTGAGGCACAGACGAACTTCACCAAGAGAGAACTGCAAGTCCTTTACCGG

GGATTCAAAAACGAGTGCCCCAGTGGTGTGGTTAACGAAGAGACATTCAAGCAGATCTACGCTCAGTTTTTCCCTCATGG

AGATGCCAGCACATACGCACATTACCTCTTCAATGCCTTCGACACCACCCAGACAGGCTCTGTAAAGTTCGAGGACTTTG

TGACTGCTCTGTCGATTTTACTGAGAGGAACGGTCCATGAAAAACTGAGGTGGACGTTTAATTTGTACGACATCAATAAA

GACGGCTACATAAACAAAGAGGAGATGATGGACATAGTGAAAGCCATCTATGACATGATGGGGAAATACACCTATCCTGT

GCTCAAAGAGGACACTCCCAGGCAGCACGTGGACGTCTTCTTCCAGAAAATGGATAAAAATAAAGATGGCATTGTAACGT

TAGACGAATTTCTCGAGTCCTGTCAGGAGGATGACAACATCATGAGGTCTCTACAGCTGTTCCAAAATGTCATGTAACTG

AGGACACTGGCCATCCTGCTCTCAGAGACACTGACAAACACCTCAATGCCCTGATCTGCCCTTGTTCCAGTTTACACAT

CAACTCTCGGGACAGAAATACCTTTTACACTTTGGAAGAATTCTCTGCTGAAGACTTTCTACAAAACCTGGCACCGAGTG

GCTCAGTCTCTGATTGCCAACTCTTCCTCCCTCCTCCTCTTGAGAGGGACGAGCTGAAATCCGAAGTTTGTTTTGGAAGC

ATGCCCATCTCTCCATGCTGCTGCTGCCCTGTGGAAGGCCCCTCTGCTTGAGCTTAAACAGTAGTGCACAGTTTTCTGCG

TATACAGATCCCCAACTCACTGCCTCTAAGTCAGGCAGACCCTGATCAATCTGAACCAAATGTGCACCATCCTCCGATGG

CCTCCCAAGCCAATGTGCCTGCTTCTCTTCCTCTGGTGGGAAGAAAGAACGCTCTACAGAGCACTTAGAGCTTACCATGA

AAATACTGGGAGAGGCAGCACCTAACACATGTAGAATAGGACTGAATTATTAAGCATGGTGGTATCAGATGATGCAAACA

GCCCATGTCATTTTTTTTTCCAGAGGTAGGGACTAATAATTCTCCCACACTAGCACCTACGATCATAGAACAAGTCTTTT

AACACATCCAGGAGGGAAACCGCTGCCCAGTGGTCTATCCCTTCTCTCCATCCCCTGCTCAAGCCCAGCACTGCATGTCT

CTCCCGGAAGGTCCAGAATGCCTGTGAAATGCTGTAACTTTTATACCCTGTTATAATCAATAAACAGAACTATTTCGTAC

AAAAAAAAAAAAAAA

FIGURE 2

RAT lvN (rlvN) PROTEIN

MLTQGESEGLQTLGIVVVLCSSLKLLHYLGLIDLSDDKIEDDLEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNEC

PSGVVNEETFKQIYAQFFPHGDASTYAHYLFNAFDTTQTGSVKFEDFVTALSILLRGTVHEKLRWTFNLYDINKDGYINK

EEMMDIVKAIYDMMGKYTYPVLKEDTPRQHVDVFFQKMDKNKDGIVTLDEFLESCQEDDNIMRSLQLFQNVM.

FIGURE 2 (cont'd)

MOUSE 1V (CD: 477-1127)

CGGCCCCCTGAGATCCAGCCCGAGCGCGGGGCGGAGCGGCCGGGTGGCAGCAGGGGCGGGCGGGCGGAGCGCAGCTCCCG

CACCGCACGCGGCGCGGGCTCGGCAGCCTCGGCCGTGCGGGCACGCCGGCCCCGTGTCCAACATCAGGCAGGCTTTGGGG

CTCGGGGCTCGGGCCTCGGAGAAGCCAGTGGCCCGGCTGGGTGCCCGCACCGGGGGGCGCCTGTC.AGGCTCCCGCGAGC

CTCTGGCCCTGGGAGTCAGTGCATGTGCCTGGCTGAAGAAGGCAGCAGCCACGAGCTCCAGGCGCCCCGGCCCCCACGTTT

TCTGAATACCAAGCTGCAGGCGAGCTGCTCGGGGCTTTTTTGCTTTCTCGCTTTTCCTCTCCTCCAATTCAAAGTGGGCA

ATCCACACCGATTTCTTTTCAGGGGAGGGAAGAGACAGGGCCTGGGGTCCCAAGACGCACACAAGTCTTCGCTGCCATGG

GGGCCGTCATGGGCACTTTCTCCTCCCTGCAGACCAAACAAAGGCGACCCTCTAAAGACAAGATTGAGGATGAGCTAGAG

ATGACCATGGTTTGCCACCGGCCTGAGGGACTGGAGCAGCTTGAGGCACAGACGAACTTCACCAAGAGAGAACTGCAAGT

CTTGTACCGGGGATTCAAAAACGAGTGCCCTAGCGGTGTGGTCAATGAAGAAACATTCAAGCAGATCTACGCTCAGTTTT

TCCCTCACGGAGATGCCAGCACATATGCACATTACCTCTTCAATGCCTTCGACACCACCCAGACAGGCTCTGTAAAGTTC

GAGGACTTTGTGACTGCTCTGTCGATTTTACTGAGAGGGACAGTCCATGAAAAACTAAGGTGGACGTTTAATTTGTATGA

CATCAATAAAGACGGCTACATAAACAAAGAGGAGATGATGGACATAGTCAAAGCCATCTATGACATGATGGGGAAATACA

CCTATCCTGTGCTCAAAGAGGACACTCCCAGGCAGCATGTGGATGTCTTCTTCCAGAAAATGGATAAAAATAAAGATGGC

ATTGTAACGTTAGATGAATTTCTTGAATCATGTCAGGAGGATGACAACATCATGAGATCTCTACAGCTGTTCCAAAATGT

CATGTAACTGAGGACACTGGCCATTCTGCTCTCAGAGACACTGACAAACACCTTAATGCCCTGATCTGCCCTTGTTCCAA

TTTTACACACCAACTCTTGGGACAGAAATACCTTTTACACTTTGGAAGAATTCTCTGCTGAAGACTTTCTACAAAACCTG

GCACCACGTGGCTCTGTCTCTGAGGGACGAGCGGAGATCCGACTTTGTTTTGGAAGCATGCCCATCTCTTCATGCTGCTG

CCCTGTGGAAGGCCCCTCTGCTTGAGCTTAATCAATAGTGCACAGTTTTATGCTTACACATATCCCCAACTCACTGCCTC

CAAGTCAGGCAGACTCTGATGAATCTGAGCCAAATGTGCACCATCCTCCGATGGCCTCCCAAGCCAATGTGCCTGCTTCT

CTTCCTCTGGTGGGAAGAAAGAGTGTTCTACGGAACAATTAGAGCTTACCATGAAAATATTGGGAGAGGCAGCACCTAAC

ACATGTAGAATAGGACTGAATTATTAAGCATGGTGATATCAGATGATGCAAATTGCCCATGTCATTTTTTTCAAAGGTAG

GGACAAATGATTCTCCCACACTAGCACCTGTGGTCATAGAGCAAGTCTCTTAACATGCCCAGAAGGGGAACCACTGTCCA

GTGGTCTATCCCTCCTCTCCATCCCCTGCTCAAACCCAGCACTGCATGTCCCTCCAAGAAGGTCCAGAATGCCTGCGAAA

CGCTGTACTTTTATACCCTGTTCTAATCAATAAACAGAACTATTTCGTAAAAAAAAAAAAAAAAAA

MOUSE 1V PROTEIN

MGAVMGTFSSLQTKQRRPSKDKIEDELEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNECPSGVVNEETFKQIYAQ

FFPHGDASTYAHYLFNAFDTTQTGSVKFEDFVTALSILLRGTVHEKLRWTFNLYDINKDGYINKEEMMDIVKAIYDMMGK

YTYPVLKEDTPRQHVDVFFQKMDKNKDGIVTLDEFLESCQEDDNIMRSLQLFQNVM.

FIGURE 3

RAT IVL DNA (CD: 31-714)

GTCCCAAGTCGCACACAAGTCTTCGCTGCCATGGGGGCCGTCATGGGTACCTTCTCGTCCCTGCAGACCCAAACAAAGGCG

ACCCTCTAAAGACATCGCCTGGTGGTATTACCAGTATCAGAGAGACAAGATCGAGGATGATCTGGAGATGACCATGGTTT

GCCATCGGCCTGAGGGACTGGAGCAGCTTGAGGCACAGACGAACTTCACCAAGAGAGAACTGCAAGTCCTTTACCGGGGA

TTCAAAAACGAGTGCCCCAGTGGTGTGGTTAACGAAGAGACATTCAAGCAGATCTACGCTCAGTTTTTCCCTCATGGAGA

TGCCAGCACATACGCACATTACCTCTTCAATGCCTTCGACACCACCCAGACAGGCTCTGTAAAGTTCGAGGACTTTGTGA

CTGCTCTGTCGATTTTACTGAGAGGAACGGTCCATGAAAAACTGAGGTGGACGTTTAATTTGTACGACATCAATAAAGAC

GGCTACATAAACAAAGAGGAGATGATGGACATAGTGAAAGCCATCTATGACATGATGGGGAAATACACCTATCCTGTGCT

CAAAGAGGACACTCCCAGGCAGCACGTGGACGTCTTCTTCCAGAAAATGGATAAAAATAAAGATGGCATTGTAACGTTAG

ACGAATTTCTCGAGTCCTGTCAGGAGGATGACAACATCATGAGGTCTCTACAGCTGTTCCAAAATGTCATGTAACTGAGG

ACACTGGCCATCCTGCTCTCAGAGACACTGACAAACACCTCAATGCCCTGATCTGCCCTTGTTCCAGTTTTACACATCAA

CTCTCGGGACAGAAATACCTTTTACACTTTGGAAGAATTCTCTGCTGAAGACTTTCTACAAAACCTGGCACCGCGTGGCT

CAGTCTCTGATTGCCAACTCTTCCTCCCTCCTCCTCTTGAGAGGGACGAGCTGAAATCCGAAGTTTGTTTTGGAAGCATG

CCCATCTCTCCATGCTGCTGCTGCCCTGTGGAAGGCCCCTCTGCTTGAGCTTAAACAGTAGTGCACAGTTTTCTGCGTAT

ACAGATCCCCAACTCACTGCCTCTAAGTCAGGCAGACCCTGATCAATCTGAACCAAATGTGCACCATCCTCCGATGGCCT

CCCAAGCCAATGTGCCTGCTTCTCTTCCTCTGGTGGGAAGAAAGAACGCTCTACAGAGCACTTAGAGCTTACCATGAAAA

TACTGGGAGAGGCAGCACCTAACACATGTAGAATAGGACTGAATTATTAAGCATGGTGGTATCAGATGATGCAAACAGCC

CATGTCATTTTTTTTCCAGAGGTAGGGACTAATAATTCTCCCACACTAGCACCTACGATCATAGAACAAGTCTTTTAACA

CATCCAGGAGGGAAACCGCTGCCCAGTGGTCTATCCCTTCTCTCCATCCCCTGCTCAAGCCCAGCACTGCATGTCTCTCC

CGGAAGGTCCAGAATGCCTGTGAAATGCTGTAACTTTTATACCCTGTTATAATCAATAAACAGAACTATTTCGTACAAAA

AAAAAAAAAAAAA

RAT IVL PROTEIN

MGAVMGTFSSLQTKQRRPSKDIAWWYYQYQRDKIEDDLEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNECPSGVV

NEETFKQIYAQFFPHGDASTYAHYLFNAFDTTQTGSVKFEDFVTALSILLRGTVHEKLRWTFNLYDINKDGYINKEEMMD

IVKAIYDMMGKYTYPVLKEDTPRQHVDVFFQKMDKNKDGIVTLDEFLESCQEDDNIMRSLQLFQNVM.

FIGURE 4

MOUSE IVL DNA (CD: 77-760)

ATCCACACCGATTTCTTTTCAGGGGAGGGAAGAGACAGGGCCTGGGGTCCCAAGACGCACACAAGTCTTCGCTGCCATGG

GGGCCGTCATGGGCACTTTCTCCTCCCTGCAGACCAAACAAAGGCGACCCTCTAAAGACATCGCCTGGTGGTATTACCAG

TATCAGAGAGACAAGATTGAGGATGAGCTAGAGATGACCATGGTTTGCCACCGGCCTGAGGGACTGGAGCAGCTTGAGGC

ACAGACGAACTTCACCAAGAGAGAACTGCAAGTCTTGTACCGGGGATTCAAAAACGAGTGCCCTAGCGGTGTGGTCAATG

AAGAAACATTCAAGCAGATCTACGCTCAGTTTTTCCCTCACGGAGATGCCAGCACATATGCACATTACCTCTTCAATGCC

TTCGACACCACCCAGACAGGCTCTGTAAAGTTCGAGGACTTTGTGACTGCTCTGTCGATTTTACTGAGAGGGACAGTCCA

TGAAAAACTAAGGTGGACGTTTAATTTGTATGACATCAATAAAGACGGCTACATAAACAAAGAGGAGATGATGGACATAG

TCAAAGCCATCTATGACATGATGGGGAAATACACCTATCCTGTGCTCAAAGAGGACACTCCCAGGCAGCATGTGGATGTC

TTCTTCCAGAAAATGGATAAAAATAAAGATGGCATTGTAACGTTAGATGAATTTCTTGAATCATGTCAGGAGGATGACAA

CATCATGAGATCTCTACAGCTGTTCCAAAATGTCATGTAACTGAGGACACTGGCCATTCTGCTCTCAGAGACACTGACAA

ACACCTTAATGCCCTGATCTGCCCTTGTTCCAATTTTACACACCAACTCTTGGGACAGAAATACCTTTTACACTTTGGAA

GAATTCTCTGCTGAAGACTTTCTACAAAACCTGGCACCACGTGGCTCTGTCTCTGAGGGACGAGCGGAGATCCGACTTTG

TTTTGGAAGCATGCCCATCTCTTCATGCTGCTGCCCTGTGGAAGGCCCCTCTGCTTGAGCTTAATCAATAGTGCACAGTT

TTATGCTTACACATATCCCCAACTCACTGCCTCCAAGTCAGGCAGACTCTGATGAATCTGAGCCAAATGTGCACCATCCT

CCGATGGCCTCCCAAGCCAATGTGCCTGCTTCTCTTCCTCTGGTGGGAAGAAAGAGTGTTCTACGGAACAATTAGAGCTT

ACCATGAAAATATTGGGAGAGGCAGCACCTAACACATGTAGAATAGGACTGAATTATTAAGCATGGTGATATCAGATGAT

GCAAATTGCCCATGTCATTTTTTTCAAAGGTAGGGACAAATGATTCTCCCACACTAGCACCTGTGGTCATAGAGCAAGTC

TCTTAACATGCCCAGAAGGGGAACCACTGTCCAGTGGTCTATCCCTCCTCTCCATCCCCTGCTCAAACCCAGCACTGCAT

GTCCCTCCAAGAAGGTCCAGAATGCCTGCGAAACGCTGTACTTTTATACCCTGTTCTAATCAATAAACAGAACTATTTCG

TACAAAAAAAAAAAAAAAAA

MOUSE IVL PROTEIN

MGAVMGTFSSLQTKQRRPSKDIAWWYYQYQRDKIEDELEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNECPSGVV

NEETFKQIYAQFFPHGDASTYAHYLFNAFDTTQTGSVKFEDFVTALSILLRGTVHEKLRWTFNLYDINKDGYINKEEMMD

IVKAIYDMMGKYTYPVLKEDTPRQHVDVFFQKMDKNKDGIVTLDEFLESCQEDDNIMRSLQLFQNVM.

FIGURE 5

RAT IVN DNA (FIRST-PASS, PARTIAL; CD: 345-955)

GTCCGGGCACACAACCCCTGGATTCTTCGGAGAATATGCCGTGACGGTGTTGCCAATTATTAGTTCTCTTGGCTAGCAGA

TGTTTAGGGACTGGTTAAGCCTTTGGAGAAATTACCTTAGGAAAACGGGGAAATAAAAGCAAAGATTACCATGAATTGCA

AGATTACCTAGCAATTGCAAGGTAGGAGGAGAGAGGTGGAGGGCGGAGTAGACAGGAGGGAGGGAGAAAGTGAGAGGAAG

CTAGGCTGGTGGAAATAACCCTGCACTTGGAACAGCGGCAAAGAAGCGCGATTTTCCAGCTTTAAATGCCTGCCCGCGTT

CTGCTTGCCTACCCGGGAACGGAGATGTTGACCCAGGGCGAGTCTGAAGGGCTCCAGACCTTGGGGATAGTAGTGGTCCT

GTGTTCCTCTCTGAAACTACTGCACTACCTCGGGCTGATTGACTTGTCGGATGACAAGATCGAGGATGATCTGGAGATGA

CCATGGTTTGCCATCGGCCTGAGGGACTGGAGCAGCTTGAGGCACAGACGAACTTCACCAAGAGAGAACTGCAAGTCCTT

TACCGGGGATTCAAAAACGAGTGCCCCAGTGGTGTGGTTAACGAAGAGACATTCAAGCNGATCTACGCTCAGTTTTTCCC

TCATGGAGATGCCAGCACATACGCACATTACCTCTTCAATGCCTTCGACACCACCCAGACAGGCTCTGTAAAGTTCGAGG

ACTTTGTGACTGCTCTGTCGATTTTACTGAGAGGAACGGTCCATGAAAAACTGAAGTGGACGTTTAATTTGTACGACATC

AATAAAGACGGCTACATAAACAAAGAGGAGATGATGGACATAGTGAAAGCCATCTATGACATGATGGGGAAATACACCTA

TCTTGTGCTCAAAGAGGACACTTCCAGGCAGCACGTGGACGTCTTCTTCCAGAAAATGGATAAAAATAAAGATGG

RAT IVN PROTEIN (PARTIAL)

MLTQGESEGLQTLGIVVVLCSSLKLLHYLGLIDLSDDKIEDDLEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNEC

PSGVVNEETFKXIYAQFFPHGDASTYAHYLFNAFDTTQTGSVKFEDFVTALSILLRGTVHEKLKWTFNLYDINKDGYINK

EEMMDIVKAIYDMMGKYTYLVLKEDTSRQHVDVFFQKMDKNKD

FIGURE 6

HUMAN 9QL DNA (CD:207-1019)

CTCACCTGCTGCCTAGTGTTCCCTCTCCTGCTCCAGGACCTCCGGGTAGACCTCAGACCCCGGGCCCATTCCCAGACTCA

GCCTCAGCCCGGACTTCCCCAGCCCCGACAGCACAGTAGGCCGCCAGGGGGCGCCGTGTGAGCGCCCTATCCCGGCCACC

CGGCGCCCCCTCCCACGGCCCGGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAGGGCCGCAAGGAGAGTTTGTCCG

ATTCCCGAGACCTGGACGGCTCCTACGACCAGCTCACGGGCCACCCTCCAGGGCCCACTAAAAAAGCGCTGAAGCAGCGA

TTCCTCAAGCTGCTGCCGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAACATTAGCCGCCCCAGCCTCCCTCCG

CCCCCACAGACCCCGCCTGCTGGACCCAGACAGCGTGGACGATGAATTTGAATTGTCCACCGTGTGTCACCGGCCTGAGG

GTCTGGAGCAGCTGCAGGAGCAAACCAAATTCACGCGCAAGGAGTTGCAGGTCCTGTACCGGGGCTTCAAGAACGAATGT

CCCAGCGGAATTGTCAATGAGGAGAACTTCAAGCAGATTTACTCCCAGTTCTTTCCTCAAGGAGACTCCAGCACCTATGC

CACTTTTCTCTTCAATGCCTTTGACACCAACCATGATGGCTCGGTCAGTTTTGAGGACTTTGTGGCTGGTTTGTCCGTGA

TTCTTCGGGGAACTGTAGATGACAGGCTTAATTGGGCCTTCAACCTGTATGACCTTAACAAGGACGGCTGCATCACCAAG

GAGGAAATGCTTGACATCATGAAGTCCATCTATGACATGATGGGCAAGTACACGTACCCTGCACTCCGGGAGGAGGCCCC

AAGGGAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGAACAAGGATGGTGTGGTGACCATTGAGGAATTCATTGAGT

CTTGTCAAAAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGACAATGTCATCTAGCCCCCAGGAGAGGGGTCAGT

GTTTCCTGGGGGGACCATGCTCTAACCCTAGTCCAGGCGGACCTCACCCTTCTCTTCCCAGGTCTATCCTCATCCTACGC

CTCCCTGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTCAGTAGTCCAGATCTCTGGAGCTGAAGGGGCCAGAGAGTGGG

CAGAGTGCATCTCGGGGGGTGTTCCCAACTCCCACCAGCTCTCACCCCCTTCCTGCCTGACACCCAGTGTTGAGAGTGCC

CCTCCTGTAGGAATTGAGCGGTTCCCCACCTCCTACCCTACTCTAGAAACACACTAGAGCGATGTCTCCTGCTATGGTGC

TTCCCCCATCCCTGACCTCATAAACATTTCCCCTAAGACTCCCCTCTCAGAGAGAATGCTCCATTCTTGGCACTGGCTGG

CTTCTCAGACCAGCCATTGAGAGCCCTGTGGGAGGGGGACAAGAATGTATAGGGAGAAATCTTGGGCCTGAGTCAATGGA

TAGGTCCTAGGAGGTGGGTGGGGTTGAGAATAGAAGGGCCTGGACAGATTATGATTGCTCAGGCATACCAGGTTATAGCT

CCAAGTTCCACAGGTCTGCTACCACAGGCCATCAAAATATAAGTTTCCAGGCTTTGCAGAAGACCTTGTCTCCTTAGAAA

TGCCCCAGAAATTTTCCACACCCTCCTCGGTATCCATGGAGAGCCTGGGGCCAGATATCTGGCTCATCTCTGGCATTGCT

TCCTCTCCTTCCTTCCTGCATGTGTTGGTGGTGGTTGTGGTGGGGGAATGTGGATGGGGGATGTCCTGGCTGATGCCTGC

CAAAATTTCATCCCACCCTCCTTGCTTATCGTCCCTGTTTTGAGGGCTATGACTTGAGTTTTTGTTTCCCATGTTCTCTA

TAGACTTGGGACCTTCCTGAACTTGGGGCCTATCACTCCCCACAGTGGATGCCTTAGAAGGGAGAGGGAAGGAGGGAGGC

AGGCATAGC

FIGURE 7

HUMAN 9QL PROTEIN

MRGQGRKESLSDSRDLDGSYDQLTGHPPGPTKKALKQRFLKLLPCCGPQALPSVSETLAAPASLRPHRPRLLDPDSVDDE

FELSTVCHRPEGLEQLQEQTKFTRKELQVLYRGFKNECPSGIVNEENFKQIYSQFFPQGDSSTYATFLFNAFDTNHDGSV

SFEDFVAGLSVILRGTVDDRLNWAFNLYDLNKDGCITKEEMLDIMKSIYDMMGKYTYPALREEAPREHVESFFQKMDRNK

DGVVTIEEFIESCQKDENIMRSMQLFDNVI

FIGURE 7 (cont'd)

RAT 9QL DNA (PARTIAL; CD: 2-775)

CCGAGATCTGGACGGCTCCTATGACCAGCTTACGGGCCACCCTCCAGGGCCCAGTAAAAAAGCCCTGAAGCAGCGTTTCC

TCAAGCTGCTGCCGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAACATTAGCTGCCCCAGCCTCCCTCCGCCCC

CACAGACCCCGCCCGCTGGACCCAGACAGCGTAGAGGATGAGTTTGAATTATCCACGGTGTGTCACCGACCTGAGGGCCT

GGAACAACTCCAGGAACAGACCAAGTTCACACGCAGAGAGCTGCAGGTCCTGTACCGAGGCTTCAAGAACGAATGCCCCA

GTGGGATTGTCAACGAGGAGAACTTCAAGCAGATTTATTCTCAGTTCTTTCCCCAAGGAGACTCCAGCAACTATGCTACT

TTTCTCTTCAATGCCTTTGACACCAACCACGATGGCTCTGTCAGTTTTGAGGACTTTGTGGCTGGTTTGTCGGTGATTCT

TCGGGGGACCATAGATGATAGACTGAGCTGGGCTTTCAACTTATATGACCTCAACAAGGACGGCTGTATCACAAAGGAGG

AAATGCTTGACATTATGAAGTCCATCTATGACATGATGGGCAAGTACACATACCCTGCCCTCCGGGAGGAGGCCCCAAGA

GAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGGAACAAGGACGGCGTGGTGACCATCGAGGAATTCATCGAGTCTTG

TCAACAGGACGAGAACATCATGAGGTCCATGCAGCTCTTTGATAATGTCATCTAGCTCCCCAGGGAGAGGGGTTAGTGTG

TCCTAGGGTGACCAGGCTGTAGTCCTAGTCCAGACGAACCTAACCCTCTCTCTCCAGGCCTGTCCTCATCTTACCTGTAC

CCTGGGGGCTGTAGGGATTCAATATCCTGGGGCTTCAGTAGTCCAGATCCCTGAGCTAAGTCACAAAAGTAGGCAAGAGT

AGGCAAGCTAAATCTGGGGGCTTCCCAACCCCCGACAGCTCTCACCCCTTCTCAACTGATACCTAGTGCTGAGGACACCC

CTGGTGTAGGGACCAAGTGGTTCTCCACCTTCTAGTCCCACTCTAGAAACCACATTAGACAGAAGGTCTCCTGCTATGGT

GCTTTCCCCATCCCTAATCTCTTAGATTTTCCTCAAGACTCCCTTCTCAGAGAACACGCTCTGTCCATGTCCCCAGCTGG

GGACATGGACAGAGCGTGTTCTCTAGTTCTAGATCGCGAGCGGCCGC

RAT 9QL PROTEIN (PARTIAL)

RDLDGSYDQLTGHPPGPSKKALKQRFLKLLPCCGPQALPSVSETLAAPASLRPHRPRPLDPDSVEDEFELSTVCHRPEGL

EQLQEQTKFTRRELQVLYRGFKNECPSGIVNEENFKQIYSQFFPQGDSSNYATFLFNAFDTNHDGSVSFEDFVAGLSVIL

RGTIDDRLSWAFNLYDLNKDGCITKEEMLDIMKSIYDMMGKYTYPALREEAPREHVESFFQKMDRNKDGVVTIEEFIESC

QQDENIMRSMQLFDNVI.

FIGURE 8

MOUSE 9QL DNA (CD: 181-993)

CGGGACTCTGAGGTGGGCCCTAAAATCCAGCGCTCCCCAGAGAAAAGCCTTGCCAGCCCCTACTCCCGGCCCCCAGCCCC

AGCAGGTCGCTGCGCGCCAGGGGGCACTGTGTGAGCGCCCTATCCTGGCCACCCGGCGCCCCCTCCCACGCCCCAGGCG

GGAGCGGGGCGCCGGGGGCCATGCGGGGCCAAGGCCGAAAGGAGATTTGTCCGAATCCCGAGATTTGGACGGCTCCTAT

GACCAGCTTACGGGCCACCCTCCAGGGCCCAGTAAAAAAGCCCTGAAGCAGCGTTTCCTCAAGCTGCTGCCGTGCTGCGG

GCCCCAAGCCCTGCCCTCAGTCAGTGAAACATTAGCTGCCCCAGCCTCCCTCCGCCCCCACAGACCCCGCCCGCTGGACC

CAGACAGCGTGGAGGATGAGTTTGAACTATCCACGGTGTGCCACCGGCCTGAGGGTCTGGAACAACTCCAGGAACAAACC

AAGTTCACACGCAGAGAGTTGCAGGTCCTGTACAGAGGCTTCAAGAACGAATGTCCCAGCGGAATTGTCAACGAGGAGAA

CTTCAAGCAAATTTATTCTCAGTTCTTTCCCCAAGGAGACTCCAGCAACTACGCTACTTTTCTCTTCAATGCCTTTGACA

CCAACCATGATGGCTCTGTCAGTTTTGAGGACTTTGTGGCTGGTTTGTCAGTGATTCTTCGGGGAACCATAGATGATAGA

CTGAACTGGGCTTTCAACTTATATGACCTCAACAAGGATGGCTGTATCACGAAGGAGGAAATGCTCGACATCATGAAGTC

CATCTATGACATGATGGGCAAGTACACCTACCCTGCCCTCCGGGAGGAGGCCCGAGGGAACACGTGGAGAGCTTCTTCC

AGAAGATGGACAGAAACAAGGACGGCGTGGTGACCATTGAGGAATTCATTGAGTCTTGTCAACAGGACGAGAACATCATG

AGGTCCATGCAACTCTTTGATAATGTCATCTAGCTCCCCAGGGAGAGGGGTTAGTGTGTCCCAGGGTAACCATGCTGTAG

CCCTAGTCCAGGCAAACCTAACCCTCCTCTCCCCGGGTCTGTCCTCATCCTACCTGTACCCTGGGGGCTGTAGGGATTCA

ACATCCTGGCGCTTCAGTAGTCCAGATCCCTGAGCTAAGTGGCGAGAGTAGGCAAGCTAAGTCTTTGGAGGGTGGGTGGG

GGCGCGCAGATTCCCAACCCCCGACGACTCTCACCCCTTTCTCGACTGATACCCAGTGCTGAGGCTACCCCTGGTGTCGG

GAACGACCAAAGTGGTTCTCTGCCTCCCCAGCCCACTCTAGAGACCCACACTAGACGGGAATATCTCCTGCTATGGTGCT

TTCCCCATCCCTGACCGCAGATTTTCCTCCTAAGACTCCCTTCTCAGAGAATATGCTTTTGTCCCTTGTCCCTGGCTGGC

TTTTCAGCCTAGCCTTTGAGGACCCTGTGGGAGGGGAGAATAAGAAAGCAGACAAAATCTTGGCCCTGAGCCAGTGGTTA

GGTCCTAGGAATCAGGCTGGAGTGGAGACCAGAAAGCCTGGGCAGGCTATGAGAGCCCCAGGTTGGCTTGTCACCGCCAG

GTTCCACAGGGCTGCTGCTCTGGGTCAGCAGAGTATGAGTTTCCAGACTTTCCAGAAGGCCTTATGTCCTTAGCAATGTC

CCAGAAATTCACCATACACTTCTCAGTGTCTTAGGATCCAGATGTCCGGTCCATCCCTGAAACCTCTCCCTCCTCCTTGC

TCCTATGGTGGGAGTGGTGGCCAGGGGACGATGAGTGAGCCGGTGTCCTGGATGATGCCTGTCAAGGTCCCACCTACCCT

CCGGCTGTCAAGCCGTTCTGGTGACCCTGTTTGATTCTCCATGACCCCTGTCTAGATGTAGAGGTGTGGAGTGAGTCTAG

TGGCAGCCTTAGGGGAATGGGAAGAACGAGAGGGGCACTCCATCTGAACCCAGTGTGGGGGCATCCATTCGAATCTTTGC

CTGGCTCCCCACAATGCCCTAGGATCCTCTAGGGTCCCCACCCCCACTCTTTAGTCTACCCAGAGATGCTCCAGAGCTCA

CCTAGAGGGCAGGGACCATAGGATCCAGGTCCAACCTGTCATCAGCATCCGGCCATGCTGCTGCTGCTTATTAATAAACC

TGCTTGTCGTTCAGCGCCCCTTCCCAGTCAGCCAGGGTCTGAGGGGAAGGCCCCCACTTTCCCGCCTCCTGTCAGACATT

GTTGACTGCTTTGCATTTTGGGCTCTTCTACCTATATTTTGTATAATAAGAAAGACACCAGATCCAATAAAACACATGGC

TATGCACAAAAAAAAAAAAAAAA

MOUSE 9QL PROTEIN

MRGQGRKESLSESRDLDGSYDQLTGHPPGPSKKALKQRFLKLLPCCGPQALPSVSETLAAPASLRPHRPRPLDPDSVEDE

FELSTVCHRPEGLEQLQEQTKFTRRELQVLYRGFKNECPSGIVNEENFKQIYSQFFPQGDSSNYATFLFNAFDTNHDGSV

SFEDFVAGLSVILRGTIDDRLNWAFNLYDLNKDGCITKEEMLDIMKSIYDMMGKYTYPALREEAPREHVESFFQKMDRNK

DGVVTIEEFIESCQQDENIMRSMQLFDNVI

FIGURE 9

HUMAN 9QM DNA (CD: 207-965)

CTCACCTGCTGCCTAGTGTTCCCTCTCCTGCTCCAGGACCTCCGGGTAGACCTCAGACCCCGGGCCCATTCCCAGACTCA

GCCTCAGCCCGGACTTCCCCAGCCCCGACAGCACAGTAGGCCGCCAGGGGGCGCCGTGTGAGCGCCCTATCCCGGCCACC

CGGCGCCCCCTCCCACGGCCCGGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAGGGCCGCAAGGAGAGTTTGTCCG

ATTCCCGAGACCTGGACGGCTCCTACGACCAGCTCACGGGCCACCCTCCAGGGCCCACTAAAAAAGCGCTGAAGCAGCGA

TTCCTCAAGCTGCTGCCGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAAACAGCGTGGACGATGAATTTGAATT

GTCCACCGTGTGTCACCGGCCTGAGGGTCTGGAGCAGCTGCAGGAGCAAACCAAATTCACGCGCAAGGAGTTGCAGGTCC

TGTACCGGGGCTTCAAGAACGAATGTCCCAGCGGAATTGTCAATGAGGAGAACTTCAAGCAGATTTACTCCCAGTTCTTT

CCTCAAGGAGACTCCAGCACCTATGCCACTTTTCTCTTCAATGCCTTTGACACCAACCATGATGGCTCGGTCAGTTTTGA

GGACTTTGTGGCTGGTTTGTCCGTGATTCTTCGGGGAACTGTAGATGACAGGCTTAATTGGGCCTTCAACCTGTATGACC

TTAACAAGGACGGCTGCATCACCAAGGAGGAAATGCTTGACATCATGAAGTCCATCTATGACATGATGGGCAAGTACACG

TACCCTGCACTCCGGGAGGAGGCCCCAAGGGAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGAAACAAGGATGGTGT

GGTGACCATTGAGGAATTCATTGAGTCTTGTCAAAAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGACAATGTCA

TCTAGCCCCCAGGAGAGGGGGTCAGTGTTTCCTGGGGGGACCATGCTCTAACCCTAGTCCAGGCGGACCTCACCCTTCTC

TTCCCAGGTCTATCCTCATCCTACGCCTCCCTGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTCAGTAGTCCAGATCTC

TGGAGCTGAAGGGGCCAGAGAGTGGGCAGAGTGCATCTCGGGGGGTGTTCCCAACTCCCACCAGCTCTCACCCCCTTCCT

GCCTGACACCCAGTGTTGAGAGTGCCCCTCCTGTAGGAATTGAGCGGTTCCCCACCTCCTACCCTACTCTAGAAACACAC

TAGAGCGATGTCTCCTGCTATGGTGCTTCCCCCATCCCTGACCTCATAAACATTTCCCCTAAGACTCCCCTCTCAGAGAG

AATGCTCCATTCTTGGCACTGGCTGGCTTCTCAGACCAGCCATTGAGAGCCCTGTGGGAGGGGGACAAGAATGTATAGGG

AGAAATCTTGGGCCTGAGTCAATGGATAGGTCCTAGGAGGTGGGTGGGGTTGAGAATAGAAGGGCCTGGACAGATTATGA

TTGCTCAGGCATACCAGGTTATAGCTCCAAGTTCCACAGGTCTGCTACCACAGGCCATCAAAATATAAGTTTCCAGGCTT

TGCAGAAGACCTTGTCTCCTTAGAAATGCCCCAGAAATTTTCCACACCCTCCTCGGTATCCATGGAGAGCCTGGGGCCAG

ATATCTGGCTCATCTCTGGCATTGCTTCCTCTCCTTCCTTCCTGCATGTGTTGGTGGTGGTTGTGGTGGGGGAATGTGGA

TGGGGGATGTCCTGGCTGATGCCTGCCAAAATTTCATCCCACCCTCCTTGCTTATCGTCCCTGTTTTGAGGGCTATGACT

TGAGTTTTTGTTTCCCATGTTCTCTATAGACTTGGGACCTTCCTGAACTTGGGGCCTATCACTCCCCACAGTGGATGCCT

TAGAAGGGAGAGGGAAGGAGGGAGGCAGGCATAGC

FIGURE 10

HUMAN 9QM PROTEIN

MRGQGRKESLSDSRDLDGSYDQLTGHPPGPTKKALKQRFLKLLPCCGPQALPSVSENSVDDEFELSTVCHRPEGLEQLQE

QTKFTRKELQVLYRGFKNECPSGIVNEENFKQIYSQFFPQGDSSTYATFLFNAFDTNHDGSVSFEDFVAGLSVILRGTVD

DRLNWAFNLYDLNKDGCITKEEMLDIMKSIYDMMGKYTYPALREEAPREHVESFFQKMDRNKDGVVTIEEFIESCQKDEN

IMRSMQLFDNVI

FIGURE 10 (cont'd)

RAT 9QM DNA (CD: 214-972)

CTCACTTGCTGCCCAAGGCTCCTGCTCCTGCCCCAGGACTCTGAGGTGGGCCCTAAAACCCAGCGCTCTCTAAAGAAAAG

CCTTGCCAGCCCCTACTCCCGGCCCCCAACCCCAGCAGGTCGCTGCGCCGCCAGGGGGCGCTGTGTGAGCGCCCTATTCT

GGCCACCCGGCGCCCCCTCCCACGGCCCAGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAAGGCAGAAAGGAGAGT

TTGTCCGAATCCCGAGATCTGGACGGCTCCTATGACCAGCTTACGGGCCACCCTCCAGGGCCCAGTAAAAAAGCCCTGAA

GCAGCGTTTCCTCAAGCTGCTGCCGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAAACAGCGTAGAGGATGAGT

TTGAATTATCCACGGTGTGTCACCGACCTGAGGGCCTGGAACAACTCCAGGAACAGACCAAGTTCACACGCAGAGAGCTG

CAGGTCCTGTACCGAGGCTTCAAGAACGAATGCCCCAGTGGGATTGTCAACGAGGAGAACTTCAAGCAGATTTATTCTCA

GTTCTTTCCCCAAGGAGACTCCAGCAACTATGCTACTTTTCTCTTCAATGCCTTTGACACCAACCACGATGGCTCTGTCA

GTTTTGAGGACTTTGTGGCTGGTTTGTCGGTGATTCTTCGGGGGACCATAGATGATAGACTGAGCTGGGCTTTCAACTTA

TATGACCTCAACAAGGACGGCTGTATCACAAAGGAGGAAATGCTTGACATTATGAAGTCCATCTATGACATGATGGGCAA

GTACACATACCCTGCCCTCCGGGAGGAGGCCCCAAGAGAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGGAACAAGG

ACGGCGTGGTGACCATCGAGGAATTCATCGAGTCTTGTCAACAGGACGAGAACATCATGAGGTCCATGCAGCTCTTTGAT

AATGTCATCTAGCTCCCCAGGGAGAGGGGTTAGTGTGTCCTAGGGTGACCAGGCTGTAGTCCTAGTCCAGACGAACCTAA

CCCTCTCTCTCCAGGCCTGTCCTCATCTTACCTGTACCCTGGGGGCTGTAGGGATTCAATATCCTGGGGCTTCAGTAGTC

CAGATCCCTGAGCTAAGTCACAAAAGTAGGCAAGAGTAGGCAAGCTAAATCTGGGGGCTTCCCAACCCCCGACAGCTCTC

ACCCCTTCTCAACTGATACCTAGTGCTGAGGACACCCCTGGTGTAGGGACCAAGTGGTTCTCCACCTTCTAGTCCCACTC

TAGAAACCACATTAGACAGAAGGTCTCCTGCTATGGTGCTTTCCCCATCCCTAATCTCTTAGATTTTCCTCAAGACTCCC

TTCTCAGAGAACACGCTCTGTCCATGTCCCCAGCTGGCTTCTCAGCCTAGCCTTTGAGGGCCCTGTGGGGAGGCGGGGAC

AAGAAAGCAGAAAAGTCTTGGCCCCGAGCCAGTGGTTAGGTCCTAGGAATTGGCTGGAGTGGAGGCCAGAAAGCCTGGGC

AGATGATGAGAGCCCAGCTGGGCTGTCACTGCAGGTTCCGGGGCCTACAGCCCTGGGTCAGCAGAGTATGAGTTCCCAGA

CTTTCCAGAAGGTCCTTAGCAATGTCCCAGAAATTCACCGTACACTTCTCAGTGTCTTAGGAGGGCCCGGGATCCAGATG

TCTGGTTCATCCCTGAATCCTCTCCCTCCTTCTTGCTCGTATGGTGGGAGTGGTGGCCAGGGGAAGATGAGTGGTGTCCC

GGATGATGCCTGTCAAGGTCCCACCTCCCCTCCGGCTGTTCTCATGACAGCTGTTTGGTTCTCCATGACCCCTATCTAGA

TGTAGAGGCATGGAGTGAGTCAGGGATTTCCCGAACTTGAGTTTTACCACTCCTCCTAGTGGCTGCCTTAGGGGAATGGG

AAGAACCCAGTGTGGGGGCACCCATTAGAATCTTTGCCCGGCTCCTCACAATGCCCTAGGGTCCCCTAGGGTACCCGCTC

CCTCTGTTTAGTCTACCCAGAGATGCTCCTGAGCTCACCTAGAGGGTAGGGACGGTAGGCTCCAGGTCCAACCTCTCCAG

GTCAGCACCCTGCCATGCTGCTGCTCCTCATTAACAAACCTGCTTGTCTCCTCCTGCGCCCCTTCTCAGTCAGCCAGGGT

CTGAGGGGAAGGGCCTCCCGTTTCCCCATCCGTCAGACATGGTTGACTGCTTTGCATTTTGGGCTCTTCTATCTATTTTG

TAAAATAAGACATCAGATCCAATAAAACACACGGCTATGCACAAAAAAAAAAAAAAAAA

RAT 9QM PROTEIN

MRGQGRKESLSESRDLDGSYDQLTGHPPGPSKKALKQRFLKLLPCGPQALPSVSENSVEDEFELSTVCHRPEGLEQLQE

QTKFTRRELQVLYRGFKNECPSGIVNEENFKQIYSQFFPQGDSSNYATFLFNAFDTNHDGSVSFEDFVAGLSVILRGTID

DRLSWAFNLYDLNKDGCITKEEMLDIMKSIYDMMGKYTYPALREEAPREHVESFFQKMDRNKDGVVTIEEFIESCQQDEN

IMRSMQLFDNVI

FIGURE 11

HUMAN 9QS DNA (CD:207-869)

CTCACCTGCTGCCTAGTGTTCCCTCTCCTGCTCCAGGACCTCCGGGTAGACCTCAGACCCCGGGCCCATTCCCAGACTCA

GCCTCAGCCCGGACTTCCCCAGCCCCGACAGCACAGTAGGCCGCCAGGGGGCGCCGTGTGAGCGCCCTATCCCGGCCACC

CGGCGCCCCCTCCCACGGCCCGGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAGGGCCGCAAGGAGAGTTTGTCCG

ATTCCCGAGACCTGGACGGCTCCTACGACCAGCTCACGGACAGCGTGGACGATGAATTTGAATTGTCCACCGTGTGTCAC

CGGCCTGAGGGTCTGGAGCAGCTGCAGGAGCAAACCAAATTCACGCGCAAGGAGTTGCAGGTCCTGTACCGGGGCTTCAA

GAACGAATGTCCCAGCGGAATTGTCAATGAGGAGAACTTCAAGCAGATTTACTCCCAGTTCTTTCCTCAAGGAGACTCCA

GCACCTATGCCACTTTTCTCTTCAATGCCTTTGACACCAACCATGATGGCTCGGTCAGTTTTGAGGACTTTGTGGCTGGT

TTGTCCGTGATTCTTCGGGGAACTGTAGATGACAGGCTTAATTGGGCCTTCAACCTGTATGACCTTAACAAGGACGGCTG

CATCACCAAGGAGGAAAATGCTTGACATCATGAAGTCCATCTATGACATGATGGGCAAGTACACGTACCCTGCACTCCGGG

AGGAGGCCCCAAGGGAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGAAACAAGGATGGTGTGGTGACCATTGAGGAA

TTCATTGAGTCTTGTCAAAAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGACAATGTCATCTAGCCCCCAGGAGA

GGGGGTCAGTGTTTCCTGGGGGGACCATGCTCTAACCCTAGTCCAGGCGGACCTCACCCTTCTCTTCCCAGGTCTATCCT

CATCCTACGCCTCCCTGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTCAGTAGTCCAGATCTCTGGAGCTGAAGGGGCC

AGAGAGTGGGCAGAGTGCATCTCGGGGGGTGTTCCCAACTCCCACCAGCTCTCACCCCCTTCCTGCCTGACACCCAGTGT

TGAGAGTGCCCCTCCTGTAGGAATTGAGCGGTTCCCCACCTCCTACCCTACTCTAGAAACACACTAGAGCGATGTCTCCT

GCTATGGTGCTTCCCCCATCCCTGACCTCATAAACATTTCCCCTAAGACTCCCCTCTCAGAGAGAATGCTCCATTCTTGG

CACTGGCTGGCTTCTCAGACCAGCCATTGAGAGCCCTGTGGGAGGGGGACAAGAATGTATAGGGAGAAATCTTGGGCCTG

AGTCAATGGATAGGTCCTAGGAGGTGGGTGGGGTTGAGAATAGAAGGGCCTGGACAGATTATGATTGCTCAGGCATACCA

GGTTATAGCTCCAAGTTCCACAGGTCTGCTACCACAGGCCATCAAAATATAAGTTTCCAGGCTTTGCAGAAGACCTTGTC

TCCTTAGAAATGCCCCAGAAATTTTCCACACCCTCCTCGGTATCCATGGAGAGCCTGGGGCCAGATATCTGGCTCATCTC

TGGCATTGCTTCCTCTCCTTCCTTCCTGCATGTGTTGGTGGTGGTTGTGGTGGGGGAATGTGGATGGGGGATGTCCTGGC

TGATGCCTGCCAAAATTTCATCCCACCCTCCTTGCTTATCGTCCCTGTTTTGAGGGCTATGACTTGAGTTTTTGTTTCCC

ATGTTCTCTATAGACTTGGGACCTTCCTGAACTTGGGGCCTATCACTCCCCACAGTGGATGCCTTAGAAGGGAGAGGGAA

GGAGGGAGGCAGGCATAGC

FIGURE 12

MONKEY 9QS DNA (CD: 133-795)

CCCACGCGTCCGCCCACGCGTCCGCGGACGCGTGGGGTGCACTAGGCCGCCAGGGGGCGCCGTGTGAGCGCCCTATCCCG

GCCACCCGGCGCCCCCTCCCACGGACCGGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAGGGCCGCAAGGAGAGTT

TGTCCGATTCCCGAGACCTGGACGGATCCTACGACCAGCTCACGGACAGCGTGGAGGATGAATTTGAATTGTCCACCGTG

TGTCACCGGCCTGAGGGTCTGGAGCAGCTGCAGGAGCAAACCAAATTCACGCGCAAGGAGTTGCAGGTCCTGTACCGGGG

CTTCAAGAACGAATGTCCGAGCGGAATTGTCAATGAGGAGAACTTCAAGCAAATTTACTCCCAGTTCTTTCCTCAAGGAG

ACTCCAGCACCTATGCCACTTTTCTCTTCAATGCCTTTGACACCAACCATGATGGCTCGGTCAGTTTTGAGGACTTTGTG

GCTGGTTTGTCCGTGATTCTTCGGGGAACTGTAGATGACAGGCTTAATTGGGCCTTCAACTTGTATGACCTCAACAAGGA

CGGCTGCATCACCAAGGAGGAAATGCTTGACATCATGAAGTCCATCTATGACATGATGGGCAAGTACACATACCCTGCAC

TCCGGGAGGAGGCCCCAAGGGAACATGTGGAGAACTTCTTCCAGAAGATGGACAGAAACAAGGATGGCGTGGTGACCATT

GAGGAATTCATTGAGTCTTGTCAAAAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGACAATGTCATCTAGCCCCC

AGGAGAGGGGGTCAGTGTTTCCTGGGGGGACCATGCTCTAACCCTAGTCCAGGTGGACCTCACCCTTCTCTTCCCAGGTC

TATCCTTGTCCTAGGCCTCCCTGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTCAGTAGTCCAGATCTCTGGAGCTGAA

GGGGCCAGAGAGTGGGCAGAGTGCATCTTGGGGGGTGTTCCCAACTCCCACCAGCTTTCACCCGCTTCCTGCCTGACACC

CAGTGTTGAGAGTGCCCCTCCTGTAGGAACTGAGTGGTTCCCCACCTCCTACCCCCACTCTAGAAACACACTAGACAGAT

GTCTCGTGCTATGGTGCTTCCCCCATCCCTGACTTCATAAACATTTCCCCTAAAACTCCCTTCTCAGAGAGAATGCTCCA

TTCTTGGCACTGGCTGGCTTCTCAGACCAGCCTTTGAGAGCCCTGTGGGAGGGGGACAAGAATGTATAGGGGAGAAATCT

TGGGCCTGAGTCAATGGATAGGTCCTAGGAGGTGGCTGGGGTTGAGAATAGAAAGGCCTGGACACAATGTGATTGCTCAG

GCATACCAAGTTATAGCTCCAAGTTCCACAGGTCTGCTACCACAGGCCATCAAAATATAAGTTTCCAGGCTTTGCAGAAG

ACCTTGTCTCCTTGGAAATGCCCCAGATATTTTCCATACCCTCCTCGATATCCATGGAGAGCCTGGGGCTAGATATCTGG

CATATCCCTGGCATTGCTTCCTCTCCTTCCTTCCTGCATGTGTTGGTGGTGGTTGTGGCAGGGGAATGTGGATAGGAGAT

GTCCTGGCAGATGCCTGCCAAAGTTTCATCCCACCCTCCCTGCTCATCGCCCCTGTTTTGAGGGCTGTGACTTGAGTTTT

TGTTTCCCATGTTCTCTATAGACTTGGGACCTTCCTGAACTTGGGGCCTATCACTCCCCACAGTGGATGCCTTAGAAGGG

AGAGGGAAGGAGGGAGGCAGGCATAGCATCTGAACCCAGTGTGGGGGCATTCACTAGGATCTTCAATCAACCCGGGCTCT

CCCCAACCCCCCAGATAACCTCCTCAGTTCCCTAGAGTCTCCTCTTGCTCTACTCAATCTACCCAGAGATGCCCCTTAGC

ACACTCAGAGGGCAGGGACCATAGGACCCAGGTTCCAACCCCATTGTCAGCACCCCAGCCATGCTGCCATCCCTTAGCAC

ACCTGCTCGTCCCATTCAGCTTACCCTCCCAGTCAGCCAGAATCTGAGGGGAGGGCCCCCAGAGAGCCCCCTTCCCCATC

AGAAGACTGTTGACTGCTTTGCATTTTGGGCTCTTCTATATATTTTGTAAAATAAGAACTATACCAGATCTAATAAAACA

CAATGGCTATGCAAAAAAAAAAAAAAAAAAA

MONKEY 9QS PROTEIN

MRGQGRKESLSDSRDLDGSYDQLTDSVEDEFELSTVCHRPEGLEQLQEQTKFTRKELQVLYRGFKNECPSGIVNEENFKQ

IYSQFFPQGDSSTYATFLFNAFDTNHDGSVSFEDFVAGLSVILRGTVDDRLNWAFNLYDLNKDGCITKEEMLDIMKSIYD

MMGKYTYPALREEAPREHVENFFQKMDRNKDGVVTIEEFIESCQKDENIMRSMQLFDNVI

FIGURE 13

RAT 9QC DNA (CD: 208-966)

TGCTGCCCAAGGCTCCTGCTCCTGCCCCAGGACTCTGAGGTGGGCCCTAAAACCCAGCGCTCTCTAAAGAAAAGCCTTGC

CAGCCCCTACTCCCGGCCCCCAACCCCAGCAGGTCGCTGCGCCGCCAGGGGGCGCTGTGTGAGCGCCCTATTCTGGCCAC

CCGGCGCCCCCTCCCACGGCCCAGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAAGGCAGAAAGGAGAGTTTGTCC

GAATCCCGAGATCTGGACGGCTCCTATGACCAGCTTACGGGCCACCCTCCAGGGCCCAGTAAAAAAGCCCTGAAGCAGCG

TTTCCTCAAGCTGCTGCCGTGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAAACAGCGTAGAGGATGAGTTTGAAT

TATCCACGGTGTGTCACCGACCTGAGGGCCTGGAACAACTCCAGGAACAGACCAAGTTCACACGCAGAGAGCTGCAGGTC

CTGTACCGAGGCTTCAAGAACGAATGCCCCAGTGGGATTGTCAACGAGGAGAACTTCAAGCAGATTTATTCTCAGTTCTT

TCCCCAAGGAGACTCCAGCAACTATGCTACTTTTCTCTTCAATGCCTTTGACACCAACCACGATGGCTCTGTCAGTTTTG

AGGACTTTGTGGCTGGTTTGTCGGTGATTCTTCGGGGGACCATAGATGATAGACTGAGCTGGGCTTTCAACTTATATGAC

CTCAACAAGGACGGCTGTATCACAAAGGAGGAAATGCTTGACATTATGAAGTCCATCTATGACATGATGGGCAAGTACAC

ATACCCTGCCCTCCGGGAGGAGGCCCCAAGAGAACACGTGGAGAGCTTCTTCCAGAAGATGGACAGGAACAAGGACGGCG

TGGTGACCATCGAGGAATTCATCGAGTCTTGTCAACAGGACGAGAACATCATGAGGTCCATGCAGCTCTCACCCCTTCTC

AACTGATACCTAGTGCTGAGGACACCCCTGGTGTAGGGACCAAGTGGTTCTCCACCTTCTAGTCCCACTCTAGAAACCAC

ATTAGACAGAAGGTCTCCTGCTATGGTGCTTTCCCCATCCCTAATCTCTTAGATTTTCCTCAAGACTCCCTTCTCAGAGA

ACACGCTCTGTCCATGTCCCCAGCTGGCTTCTCAGCCTAGCCTTTGAGGGCCCTGTGGGGAGGCGGGGACAAGAAAGCAG

AAAAGTCTTGGCCCCGAGCCAGTGGTTAGGTCCTAGGAATTGGCTGGAGTGGAGGCCAGAAAGCCTGGGCAGATGATGAG

AGCCCAGCTGGGCTGTCACTGCAGGTTCCGGGGCCTACAGCCCTGGGTCAGCAGAGTATGAGTTCCCAGACTTTCCAGAA

GGTCCTTAGCAATGTCCCAGAAATTCACCGTACACTTCTCAGTGTCTTAGGAGGGCCCGGGATCCAGATGTCTGGTTCAT

CCCTGAATCCTCTCCCTCCTTCTTGCTCGTATGGTGGGAGTGGTGGCCAGGGGAAGATGAGTGGTGTCCCGGATGATGCC

TGTCAAGGTCCCACCTCCCCTCCGGCTGTTCTCATGACAGCTGTTTGGTTCTCCATGACCCCTATCTAGATGTAGAGGCA

TGGAGTGAGTCAGGGATTTCCCGAACTTGAGTTTTACCACTCCTCCTCATAGTGGCTGCCTTAGGGGAATGGGAAGAACCCAG

TGTGGGGGCACCCATTAGAATCTTTGCCCGGCTCCTCACAATGCCCTAGGGTCCCCTAGGGTACCCGCTCCCTCTGTTTA

GTCTACCCAGAGATGCTCCTGAGCTCACCTAGAGGGTAGGGACGGTAGGCTCCAGGTCCAACCTCTCCAGGTCAGCACCC

TGCCATGCTGCTGCTCCTCATTAACAAACCTGCTTGTCTCCTCCTGCGCCCCTTCTCAGTCAGCCAGGGTCTGAGGGGAA

GGGCCTCCCGTTTCCCCATCCGTCAGACATGGTTGACTGCTTTGCATTTTGGGCTCTTCTATCTATTTTGTAAAATAAGA

CATCAGATCCAATAAAACACACGGCTATGCACAAAAAAAAAAAAAAAAAAAAAAAA

RAT 9QC PROTEIN

MRGQGKKESLSESRDLDGSYDQLTGHPPGPSKKALKQRFLKLLPCCGPQALPSVSENSVEDEFELSTVCHRPEGLEQLQE

QTKFTRRELQVLYRGFKNECPSGIVNEENFKQIYSQFFPQGDSSNYATFLFNAFDTNHDGSVSFEDFVAGLSVILRGTID

DRLSWAFNLYDLNKDGCITKEEMLDIMKSIYDMMGKYTYPALREEAPREHVESFFQKMDRNKDGVVTIEEFIESCQQDEN

IMRSMQLSPLLN.

FIGURE 14

RAT 8T (9Q SPLICE VARAIANT) DNA (MAY NOT BE FULL LENGTH, CD: 1-678)

ATGAACCACTGCCCTCGCAGGTGCCGGAGCCCGTTGGGGCAGGCAGCTCGATCTCTCTACCAGTTGGTAACTGGGTCGCT

GTCGCCAGACAGCGTAGAGGATGAGTTTGAATTATCCACGGTGTGTCACCGACCTGAGGGCCTGGAACAACTCCAGGAAC

AGACCAAGTTCACACGCAGAGAGCTGCAGGTCCTGTACCGAGGCTTCAAGAACGAATGCCCCAGTGGGATTGTCAACGAG

GAGAACTTCAAGCAGATTTATTCTCAGTTCTTTCCCCAAGGAGACTCCAGCAACTATGCTACTTTTCTCTTCAATGCCTT

TGACACCAACCACGATGGCTCTGTCAGTTTTGAGGACTTTGTGGCTGGTTTGTCGGTGATTCTTCGGGGGACCATAGATG

ATAGACTGAGCTGGGCTTTCAACTTATATGACCTCAACAAGGACGGCTGTATCACAAAGGAGGAAATGCTTGACATTATG

AAGTCCATCTATGACATGATGGGCAAGTACACATACCCTGCCCTCCGGGAGGAGGCCCCAAGAGAACACGTGGAGAGCTT

CTTCCAGAAGATGGACAGGAACAAGGACGGCCGTGGTGACCATCGAGGAATTCATCGAGTCTTGTCAACAGGACGAGAACA

TCATGAGGTCCATGCAGCTCTTTGATAATGTCATCTAGCTCCCCAGGGAGAGGGGTTAGTGTGTCCTAGGGTGACCAGGC

TGTAGTCCTAGTCCAGACGAACCTAACCCTCTCTCTCCAGGCCTGTCCTCATCTTACCTGTACCCTGGGGGCTGTAGGGA

TTCAATATCCTGGGGCTTCAGTAGTCCAGATCCCTGAGCTAAGTCACAAAAGTAGGCAAGAGTAGGCAAGCTAAATCTGG

GGGCTTCCCAACCCCCGACAGCTCTCACCCCTTCTCAACTGATACCTAGTGCTGAGGACACCCCTGGTGTAGGGACCAAG

TGGTTCTCCACCTTCTAGTCCCACTCTAGAAACCACATTAGACAGAAGGTCTCCTGCTATGGTGCTTTCCCCATCCCTAA

TCTCTTAGATTTTCCTCAAGACTCCCTTCTCAGAGAACACGCTCTGTCCATGTCCCCAGCTGGCTTCTCAGCCTAGCCTT

TGAGGGCCCTGTGGGGAGGCGGGGACAAGAAAGCAGAAAAGTCTTGGCCCCGAGCTAGTGGTTAGGTCCTAGGAATTGGC

TGGAGTGGAGGCCAGAAAGCCTGGGCAGATGATGAGAGCCCAGCTGGGCTGTCACTGCAGGTTCCAGGGCCTACAGCCCT

GGGTCAGCAGAGTATGAGTTCCCAGACTTTCCAGAAGGTCCTTAGCAATGTCCCAGAAATTCACCATACACTTCTCAGTG

TCCCGGATGATGCCTGTCAAGGTCCCACCTCCCCTCCGGCTGTTCTCATGACAGCTGTTTGGTTCTCCATGACCCCTATC

TAGATGTAGAGGCATGGAGTGAGTCAGGGATTTCCCGAACTTGAGTTTTACCACTCCTCCTAGTGGCTGCCTTAGGGGAA

TGGGAAGAACCCAGTGTGGGGGCACCCATTAGAATCTTTGCCCGGTTCCTCACAATGCCCTAGGGTCCCCTAGGGTACCC

GCTCCCTCTGTTTAGTCTACCCAGAGATGCTCCTGAGCTCACCTAGAGGGTAGGGACGGTAGGCTCCAGGTCCAACCTCT

CCAGGTCAGCACCCTGCCATGCTGCTGCTCCTCATTAACAAACCTGCTTGTCTCCTCCTGCGCCCTTCTCAGTCAGCCA

GGGTCTGAGGGGAAGGGCCTCCCGTTTCCCCATCCGTCAGACATGGTTGACTGCTTTGCATTTTGGGCTCTTCTATCTAT

TTTGTAAAATAAGACATCAGATCCAATAAAACACACGGCTATGCACAAAAAAAAAAAAAAAAA

RAT 8T (9Q SPLICE VARAIANT) PROTEIN (MAY NOT BE FULL LENGTH)

MNHCPRRCRSPLGQAARSLYQLVTGSLSPDSVEDEFELSTVCHRPEGLEQLQEQTKFTRRELQVLYRGFKNECPSGIVNE

ENFKQIYSQFFPQGDSSNYATFLFNAFDTNHDGSVSFEDFVAGLSVILRGTIDDRLSWAFNLYDLNKDGCITKEEMLDIM

KSIYDMMGKVTYPALREEAPREHVESFFQKMDRNKDGVVTIEEFIESCQQDENIMRSMQLFDNVI

FIGURE 15

>human KChIP3 cds = 1-7.

ATGCAGCCGGCTAAGGAAGTGACAAAGGCGTCGGACGGCAGCCTCCTGGGGGACCTCGGGC
ACACACCACTTAGCAAGAA
GGAGGGTATCAAGTGGCAGAGGCCGAGGCTCAGCCGCCAGGCTTTGATGAGATGCTGCCTG
GTCAAGTGGATCCTGTCCA
GCACAGCCCCACAGGGCTCAGATAGCAGCGACAGTGAGCTGGAGCTGTCCACGGTGCGCCA
CCAGCCAGAGGGGCTGGAC
CAGCTGCAGGCCCAGACCAAGTTCACCAAGAAGGAGCTGCAGTCTCTCTACAGGGGCTTTA
AGAATGAGTGTCCCACGGG
CCTGGTGGACGAAGACACCTTCAAACTCATTTACGCGCAGTTCTTCCCTCAGGGAGATGCCA
CCACCTATGCACACTTCC
TCTTCAACGCCTTTGATGCGGACGGGAACGGGGCCATCCACTTTGAGGACTTTGTGGTTGGC
CTCTCCATCCTGCTGCGG
GGCACAGTCCACGAGAAGCTCAAGTGGGCCTTTAATCTCTACGACATTAACAAGGATGGCT
ACATCACCAAAGAGGAGAT
GCTGGCCATCATGAAGTCCATCTATGACATGATGGGCCGCCACACCTACCCCATCCTGCGGG
AGGACGCGCCGGCGGAGC
ACGTGGAGAGGTTCTTCGAGAAAATGGACCGGAACCAGGATGGGGTAGTGACCATTGAAGA
GTTCCTGGAGGCCTGTCAG
AAGGATGAGAACATCATGAGCTCCATGCAGCTGTTTGAGAATGTCATCTAGgacacgtccaaaggagt
gcatggccacag

ccacctccaccccccaagaaacctccatcctgccaggagcagcctccaagaaacttttaaaaaaatagatttgcaaaaagtg
aacagattgctacacacacacacacacacacacacacacacacacacacacacacagccattcatctgggctggcagaggggac
agagttcagggaggggctgagtctggctagggccgagtccaggagccccagccagcccttcccaggccagcgaggcgag
gctgcctctgggtgagtggctgacagagcaggtctgcaggccaccagctgctggatgtcaccaagaaggggctcgagtgc
ccctgcaggggaggctccaatctccggtgtgagcccacctcgtccgttctccattctgctttcttgccacacagtgggc
cggccccaggctccctggtctcctccccgtagccactctctgcccactacctatgcttctagaaagcccctcacctcag
gaccccagagggaccagctgggggcaggggggagaggggtaatggaggccaagcctgcagctttctggaaattcttcc
ctgggggtcccaggatccctgctactccactgacctggaagagctgggtaccaggccacccactgtggggcaagcctga
gtggtgaggggccactgggccccattctccctccatggcaggaaggcgggggatttcaagtttaggggattgggtcgtggt
ggagaatctgagggcactctctgccagctccacagggtgggatgagcctctccttgccccagtcctggttcagtgggaat
gcagtgggtggggctgtacacaccctccagcacagactgttccctccaaggtcctcttaggtcccgggaggaacgtggtt
cagagactggcagccaggggagcccggggcagagctcagaggagtctgggaaggggcgtgtccctcctcttcctgtagtgc
cctcccatggcccagcagcttggctgagccccctctcctgaagcagtgtcgccgtccctctgccttgcacaaaaagcac
aagcattccttagcagctcaggcgcagccctagtgggagcccagcacactgcttctcggaggccaggccctcctgctggc
tgaggcttgggcccagtagccccaatatggtggccctggggaagaggccttgggggtctgctctgtgcctgggatcagtg
gggccccaaagcccagcccggctgaccaacattcaaaagcacaaacctggggactctgcttggctgtcccctccatctg
ggcatggagaatgccagcccaaagctggagccaatggtgaggctgagaggctgtggctgggtggtcagcagaaacccc
caggaggagagagatgctgctccgcctgattgggcctcacccagaaggaacccggtcccaggccgcatggccctcca
ggaacattcccacataatacattccatcacagccagcccagctccactcagggctggcccgggagtcccctgtgtcccc
aagaggctagccccagggtgagcagggccctcagaggaaaggcagtatggcggaggccatgggggcccctcggcattcac
acacagcctggcctcccctgcggagctgcatggacgcctggctccaggctccaggctgactgggggcctctgcctccagg
agggcatcagctttccctggctcaggatcttctccctccctcacccgctgcccagccctcccagctggtgtcactctg
cctctaaggccaaggcctcaggagagcatcaccaccacacccctgccggccttggccttgggccagactggctgcacag
cccaaccaggaggggtctgcctcccacgctgggacacagcaccggccgcatgtctgcatggcagaagcgtctccctggcc
acggcctgggagggtggttcctgttctcagcatccactaatatttcagtcctgtatattttaataaaataaacttgacaaa
ggaaaaaaaaaaaaaaaaaattcctgcggccgcgttctcca

FIGURE 16

>human KChIP3
MQPAKEVTKASDGSLLGDLGHTPLSKKEGIKWQRPRLSRQALMRCCLVKWILSSTAPQGSDSSD
SELELSTVRHQPEGLD
QLQAQTKFTKKELQSLYRGFKNECPTGLVDEDTFKLIYAQFFPQGDATTYAHFLFNAFDADGNG
AIHFEDFVVGLSILLR
GTVHEKLKWAFNLYDINKDGYITKEEMLAIMKSIYDMMGRHTYPILREDAPAEHVERFFEKMD
RNQDGVVTIEEFLEACQ
KDENIMSSMQLFENVI

FIGURE 16 (cont'd)

RAT P19 DNA (FIRST-PASS, PARTIAL; CD:1-330)
TTTGAGGACTTTGTGGTTGGGCTCTCCATCCTGCTTCGAGGGACCGTCCATGAGAAGCTCAAGTGGGCCTTCAATCTCTA

CGACATCAACAAGGACGGTTACATCACCAAAGAGGAGATGCTGGCCATCATGAAGTCCATCTACGACATGATGGGCCGCC

ACACCTACCCTATCCTGCGGGAGGACGCACCTCTGGAGCATGTGGAGAGGTTCTTCCAGAAAATGGACAGGAACCAGGAT

GGAGTAGTGACTATTGATGAATTTCTGGAGACTTGTCAGAAGGACGAGAACATCATGAGCTCCATGCAGCTGTTTGAGAA

CGTCATCTAGGACATGTAGGAGGGGACCCTGGGTGGCCATGGGTTCTCAACCCAGAGAAGCCTCAATCCTGACAGGAGAA

GCCTCTATGAGAAACATTTTTCTAATATATTTGCAAAAAGTG

RAT P19 PROTEIN (PARTIAL)
FEDFVVGLSILLRGTVHEKLKWAFNLYDINKDGYITKEEMLAIMKSIYDMMGRHTYPILREDAPLEHVERFFQKMDRNQD

GVVTIDEFLETCQKDENIMSSMQLFENVI

FIGURE 17

MOUSE P19 DNA (CD: 49-819)

CGGGCTGCAAAGCGGGAAGATTAGTGACGGTCCCTTTCAGCAGCAGAGATGCAGAGGACCAAGGAAGCCGTGAAGGCATC

AGATGGCAACCTCCTGGGAGATCCTGGGCGCATACCACTGAGCAAGAGGGAAAGCATCAAGTGGCAAAGGCCACGGTTCA

CCCGCCAGGCCCTGATGCGTTGCTGCTTAATCAAGTGGATCCTGTCCAGTGCTGCCCCACAAGGCTCAGACAGCAGTGAC

AGTGAACTGGAGTTATCCACGGTGCGCCATCAGCCAGAGGGCTTGGACCAGCTACAAGCTCAGACCAAGTTCACCAAGAA

GGAGCTGCAGTCCCTTTACCGAGGCTTCAAGAATGAGTGTCCCACAGGCCTGGTGGATGAAGACACCTTCAAACTCATTT

ATTCCCAGTTCTTCCCTCAGGGAGATGCCACCACCTATGCACACTTCCTCTTCAATGCCTTTGATGCTGATGGGAACGGG

GCCATCCACTTTGAGGACTTTGTGGTTGGGCTCTCCATCCTGCTTCGAGGGACGGTCCATGAGAAGCTCAAGTGGGCCTT

CAATCTCTATGACATTAACAAGGATGGTTGCATCACCAAGGAGGAGATGCTGGCCATCATGAAGTCCATCTACGACATGA

TGGGCCGCCACACCTACCCCATCCTGCGGGAGGATGCACCCCTGGAGCATGTGGAGAGGTTCTTTCAGAAAATGGACAGG

AACCAGGATGGAGTGGTGACCATTGATGAATTTCTGGAGACTTGTCAGAAGGATGAGAACATCATGAACTCCATGCAGCT

GTTTGAGAACGTCATCTAGGACATGTGGGAGGGGACCCCAGTGGTCATTGCTTCTCAACCCAGAGAAGCCTCAATCCTGA

CAGGAGAAGCCTCTATGAGAAACATTTTTCTAATATATTTGCAAAAAGTGAGCAGTTTACTTCCAAGACACAGCCACCGT

CACACACAGACACAGACATACAGACACACACACACACACACACATGGTTCCTCTGGCTTGGCCAAGGAAGTGGCAGCC

AGAAGGCACCCCCGCCTATTCCTAGGTCAATAAAAAAGGCTGCCTCTGGGATGGCCAGCCCTGGCTAGATGTTACCCACA

AGGAACTCAGAGATCGAGAGGACCAGGTCTACAAAGCTAAGGTCCCTGTGTCTTTTCTACCACTCGGGAGATCAAACTAC

TCCCTGCCTATGGACCCATGCTCTTAGGAAGCTCCCAGAAACTCCAAGGGGACAAAGAGGGGAGAGGTCTATAGGAAGAA

ATGGTTTTGGAAGCTGGGCTTGCAGCCTTATGCTAATGATCACCTGGGGTCCTGGAACCCGAGTGCCAGGCTACCTACTA

TGCCGTGAGCTTAGATAGTGAGGGGCCATTGGACTAAGACCTCCTGTAAGAGTGGGGCAGGATTGAGGTTTTTGGAGAAA

CTGAGGAAACAATTTGTCCATACCACTGGGTGAAGACTGCTGGCCAGTGGGAATGTGGCTGGTGGAGATTTCCCAACTTC

CAGCACCAGGATGGCCTCTCCAAGGTCCTCTTTGATTCCCTGGGGAGATCACCTGGCTCATAGACTGACAACCAGGGAAC

TGGGCTGAAATGGGAGGTCTGGTAGGGGGCATCCCCCTCCTTTTCCCTGGCCACTTGCCACCCAGTTCCTTAACACAGTG

GATCGGCCACACCTCTGTGGCTGCCCTTGAACAGACTCATCCCGACCAAGACAAAAAAGCACAAACTCCTAGCAGCTCAG

GCCAAGCCCACAAGGGAAGGCCTGGGTCCCTGCAGCCCTGATTCAGTGGCCGAGGAAGACGCTCAGACATCCATCCTGTA

CCTCGGAGCCTTGGGGGTCTCACAGCCCTTTCCCAGCCCAGCTCGCCAACATTCTAAAGCACAAACCTGCGGATTCTGCT

TGCTTGGGCTGCGCCCTGGGGATTGAAGGCCACTGTTAACCCTAAGCTGGAGCTAGCCCTGAGGGCTGGGGACCTGTGAC

CAGGCAACAGGTCAGCAGACCCTCAGGAGGAGAGAGAGCTGTTCCTGCCTCCCCAGGCCTCGCCCAGAAGGAACAGTGTC

CCAAGAAGCATGTTTCCTGGAGGAACATCCCCACAAAAGTACATTCCATCATCTGAAGCCCGGTCTCTGCTCAGGCCTGC

CTCTGAAAGTCCACGTGTGTTCCCCAGAAGGCCAGCCCCAAGATAAGGGAGGTCCTTAGAGGAAGGACAGGGTGACAACA

CCCCTATACACAGGTGGACCCCCCCCTCTGAGGACTGTACTGACCCCATCTCCATCCTGACCGGGGCCTTCCTTTACCCGA

TCTACAGACCACCAGTTCTCCCTGGCTCAGGGACCCCCTGTCCCCCAGTCTGACTCTTCCCATCGAGGTCCCTGTCTTGT

GAAAAGCCAAGGCCACGGGAAAAGGCCACCACTCTAACCTGCTGCATCCCTTAGCCTCTGGCTGCACGCCCAACCTGGAG

GGGTCTGTCCCCTTTGCAGGGACACAGACTGGCCGCATGTCCGCATGGCAGAAGCGTCTCCCTTGGGTGCAGCCTGGAAG

GGTGGTTTCTGTCTCAGCGCCCACCAATATTCAGTCCTATATATTTTAATAAAAGAAACTTGACAAAGGAAAAAAAAAAA

AAAA

FIGURE 18

>AI 352454 (partial) cds = 1-339
CACGAGGTGGAAAGCATTTCGGCTCAGCTGGAGGAGGCCAGCTCTACAGGCGGTTTCCTGT
ACGCTCAGAACAGCACCAA
GCGCAGCATTAAAGAGCGGCTCATGAAGCTCTTGCCCTGCTCAGCTGCCAAAACGTCGTCTC
CTGCTATTCAAAACAGCG
TGGAAGATGAACTGGAGATGGCCACCGTCAGGCATCGGCCCGAAGCCCTTGAGCTTCTGGA
AGCCCAGAGCAAATTTACC
AAGAAAGAGCTTCAGATCCTTTACAGAGGATTTAAGAACGTAAGAACTTTCTTTTTGACTTT
ACCTTCACACAATTCCCA
GAGGAGCATTGAGAAATGAgaggaaaagggggaaaatatcccattctatgagaagccccatcatatgtatatttcatact
gatccttcccagataggaatataatcagtatctgtggactttgaatctctgtggcacacccatgctggcatactgtaatt
gcccattaaacaaanagtttttgagaaaaaaaaaaaaaaaaaaaaaaaa

>AI352454
HEVESISAQLEEASSTGGFLYAQNSTKRSIKERLMKLLPCSAAKTSSPAIQNSVEDELEMATVRHR
PEALELLEAQSKFT
KKELQILYRGFKNVRTFFLTLPSHNSQRSIEK

FIGURE 19

P193 (AA349365) DNA (CD: 2-127, partial)

TGAAAGGTTCTTCGAGAAAATGGACCGGAACCAGGATGGGGTAGTGACCATTGAAGAGTTCCTGGAGGC
CTGTCAGAAGGATGAGAACATCATGAGCTCCATGCAGCTGTTTGAGAATGTCATCTAGGACACGTCCAAA
GGAGTGCATGGCCACAGCCACCTCCACCCCCAAGAAACCTCCATCCTGCCAGGAGCAGCCTCCAAGAAA
CTTTTAAAAAATAGATTTGCAAAAAGTGAACAGATTGCTACACACACACACACACACACACACACAC
ACACACACACGCCATTCATCTGGGCTGGCAGAGGGGACAGAGTTCAGGGAGGGGCTGAGTCTGGCTAG
GGGCCGAGTCCAGGAGCCCCAGCCAGCCCTTCCCAGGCCAGCGAGGCGAGGCTGCCTCTGGGTGAGTGG
CTGACAGAGCAGGTCTGCAGGCCACCAGCTGCTGGATGTCACCAAGAAGGGGCTCGAGTGCCCCTGCAG
GGGAGGGTCCAATCTCCGGTGTGAGCCCACCTCGTCCCGTTCTCCATTCTGCTTTCTTGCCACACAGTGGG
CCGGCCCCAGGCTCCCCTGGTCTCCTCCCCGTAGCCACTCTCTGCCCACTACCTATGCTTCTAGAAAGCCC
CTCACCTCAGGACCCCAGAGGGACCAGCTGGGGGGCAGGGGGAGAGGGGGTAATGGAGGCCAAGCCT
GCAGCTTTCTGGAAATTCTTCCCTGGGGGTCCCAGGATCCCCTGCTACTCCACTGACCTGGAAGAGCTGG
GTACCAGGCCACCCACTGTGGGGCAAGCCTGAGTGGTGAGGGGCCACTGGGCCCCATTCTCCCTCCATGG
CAGGAAGGCGGGGGATTTCAAGTTTAGGGATTGGGTCGTGGTGGAGAATCTGAGGGCACTCTCTGCCAG
CTCCACAGGGTGGGATGAGCCTCTCCTTGCCCCAGTCCTGGTTCAGTGGGAATGCAGTGGGTGGGGCTGT
ACACACCCTCCAGCACAGACTGTTCCCTCCAAGGTCCTCTTAGGTCCCGGGAGGAACGTGGTTCAGAGAC
TGGCAGCCAGGGAGCCCGGGGCAGAGCTCAGAGGAGTCTGGGAAGGGGCGTGTCCCTCCTCTTCCTGTA
GTGCCCCTCCCATGGCCCAGCAGCTTGGCTGAGCCCCCTCTCCTGAAGCAGTGTCGCCGTCCCTCTGCCTT
GCACAAAAAGCACAAGCATTCCTTAGCAGCTCAGGCGCAGCCCTAGTGGGAGCCCAGCACACTGCTTCT
CGGAGGCCAGGCCCTCCTGCTGGCTGAGGCTTGGGCCCAGTAGCCCCAATATGGTGGCCCTGGGGAAGA
GGCCTTGGGGGTCTGCTCTGTGCCTGGGATCAGTGGGGCCCCAAAGCCCAGCCCGGCTGACCAACATTCA
AAAGCACAAACCCTGGGGACTCTGCTTGGCTGTCCCCTCCATCTGGGGATGGAGAATGCCAGCCCAAAG
CTGGAGCCAATGGTGAGGGCTGAGAGGGCTGTGGCTGGGTGGTCAGCAGAAACCCCCAGGAGGAGAGA
GATGCTGCTCCCGCCTGATTGGGGCCTCACCCAGAAGGAACCCGGTCCCAGGCCGCATGGCCCCTCCAGG
AACATTCCCACATAATACATTCCATCACAGCCAGCCCAGCTCCACTCAGGGCTGGCCCGGGGAGTCCCCG
TGTGCCCCAAGAGGCTAGCCCCAGGGTGAGCAGGGCCCTCAGAGGAAAGGCAGTATGGCGGAGGCCATG
GGGGCCCCTCGGCATTCACACACAGCCTGGCCTCCCCTGCGGAGCTGCATGGACGCCTGGCTCCAGGCTC
CAGGCTGACTGGGGGCCTCTGCCTCCAGGAGGGCATCAGCTTTCCCTGGCTCAGGGATCTTCTCCCTCCC
CTCACCCGCTGCCCAGCCCTCCCAGCTGGTGTCACTCTGCCTCTAAGGCCAAGGCCTCAGGAGAGCATCA
CCACCACACCCCTGCCGGCCTTGGCCTTGGGGCCAGACTGGCTGCACAGCCCAACCAGGAGGGGTCTGC
CTCCCACGCTGGGACACAGACCGGCCGCATGTCTGCATGGCAGAAGCGTCTCCCTTGGCCACGGCCTGGG
AGGGTGGTTCCTGTTCTCAGCATCCACTAATATTCAGTCCTGTATATTTTAATAAAATAAACTTGACAAAG
GAAAAAAAAAAAAAAAAAA

P193 PROTEIN (PARTIAL)

ERFFEKMDRNQDGVVTIEEFLEACQKDENIMSSMQLFENVI

FIGURE 20

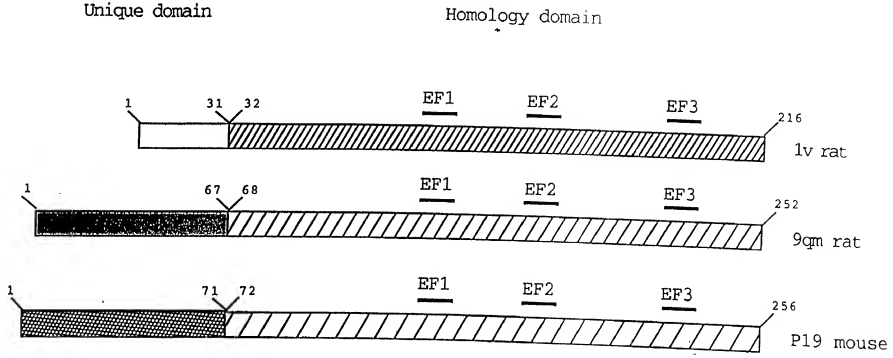

Diagram to indicate homology and uniqueness among rat 1v, rat 9qm, and mouse p19 proteins. Numbers: amino acid positions.

The C-terminal 185 amino acids are conserved (hatched lines). The homologies among the homology domains are:
rat 1v vs rat 9q: 74%
rat 1v vs mouse P19: 71%
rat 9q vs mouse P19: 75%

The N-termini are distinct (open and shaded boxes).

The putative calcium-binding EF-hand motifs conserved in all are represented as solid bars

FIGURE 21

Human 9q genomic DNA sequences:

A. exon1 sequence (with introns included):

CGGGAGGAGAGAGGCAGCTCGGCTCGGCTCCGCGCTCAGCTCCGCTCTGCCTCCGGCTCTGCGCTCACCTGCTGCCT
AGTGTTCCCTCTCCTGCTCCAGGACCTCCGGGTAGACCTCAGACCCCGGGCCCATTCCCAGACTCAGCCTCAGCCCG
GACTTCCCCAGCCCCGACAGCACAGTAGGCCGCCAGGGGGCGCCGTGTGAGCGCCCTATCCCGGCCACCCGGCGCCC
CCTCCCACGGCCCGGGCGGGAGCGGGGCGCCGGGGGCCATGCGGGGCCAGGGCCGCAAGGAGAGTTTGTCCGATTCC
CGAGACCTGGACGGCTCCTACGACCAGCTCACGGGTGAGTCAGTGACGTGGGGTCGCGGAGGAGGGGTGGATTCC
ATTCCTCCAGACCCTTCCGCCTCTCCGACCCCGGCCTGGCCCGCACCAACACTCTGCCCCATTCCCAGGCACTCTTA
TGGCCGGTCTGGGCGGCAGGACACTGGGGGTTCAAAGCCTTGGGTCCCGCAGGGGTTGGGGAGGAACAGAAGAGGCA
GGTGTGGAGAGGCAGCAGGTGTGGGCGTATGTGACACAGGGCTGAGAGGGTGTCTGGAGTGGGAGGTGTTACCGTGC
GTGAGCACCTGTCATTCTGTGTGTGTGTGTGTGCGCGCGCACCTCCCACAGCTGGTTGCCATGTGCCCTGGGC
TTGGTGACAGCTAGGGTGAGTGTGATTGTATGTGGCAGTGCAATTGTATGGTCTCGTCAGATGTTTGAGTTTGCGTA
GGACCCTGGTTGTACTGATGAAGTTGTTTTGACCATGTGTCTYTATGTGCAACGATGTGTTGTGAGTGTGTAATTCT
GTATGAAAGTGGTGTGTAACTACCAGAATGTGTCAGGGCTCTACTTTAGGGTGGCTTGTCTCTTTG

B. Exon 2-11 sequence (with introns included):

AGCCNANTGGGTCNCCATGTGTATGCATCCTGTTTACTTAGGTCACATTTGTATATGTTGTGTAAGGAGTACCAGGT
CAATGTGTGTGTGTGTGAGCATGNATAAACGCCANCAGGTGTGAGTTANTGAATATCAAGCTGTCACTGGCACCC
ATCACTGTGATGTATTGTTCATACATGTCACNAACACGGCCTGTCACTGTAGGTGTGTGTATRAGAGAGGTGTTCTT
ACCCAGGCAATCCTTGGGTTGGACATCATCNTGAGAGGTCCAGCCATGGCACTTGAGCCAAGGGTACTAGGTCAGCA
AAGACATTGAGGCCACTGCCACCTCATCCTTGCCGCCTCGCTGTCACCGGCCACGTCCCATTAAACCAAGTGCNTGA
GCCTCACCTCTATGGACTCACTGGGCTCCCCTAACCCGATTCCAACCACCCTTGCCATTCCTTTCCTCCCCTTAATT
CCTCCCCCAGCCCGGTCCCCAGATGGGGTTGATTTGTGACTGGCGGGGAGGGGACAGGGAACAGAGGGACCCCGGGA
GTTAATGTGCCTTCCTGGGGTCTTCTCTCTTCNCAGGCCACCCTCCAGGGCCCACTCAAAAAAGCGCTGAAGCAGCGA
TTCCTCAAGCTGCTGCCGAGCTGCGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAAGCAAGTGCCTCTCATGTGCTTC
CCGGGGCGGGGCTCGATGTGTGCGTGCGTGTCTGTGCATGANTGTGTGCGCGTGTGCCCAGGCCTGCRAGTGTKCS
CATGYTCCAGGCTTGCATGTGTGGGGGGGCGTGCCCCAAGCCTKSGTGTTTGGGGGTGGGGCCTGCCCCAVGCCTGT
GCGTGTGTATGTGTGTGCATGTGCGCRCGAGCGTRCCCCAGACCGGCGTGTGTGTGTGGGGGCGTGCCCTACCCC
TGCATGTGTGTGGAGGGCGTGCCCCAKGCCCKCGGCGNGTTGTTTGTTGTGTATGGGAAGGCGTACCGCACGCCTGC
GTGTGGGGGAGGGGCGTGCCCCAGAGCCTGCGTGCGTGTGTGTGTGTGTGTGTGTGTGGTGGGCGTGACCAGCG
TGGCGAGGGCGGGTGCTGGCAAGGCTGGAGCATAAGNGGGCGNGGCTACATGTGTGNGTGTACGNCTGAAGCCAGCG
TGTGTGGGCGTGGTCAGTTGGNAGCGGGTGTGTGTCACCGCTCCCGCAAAACTGTGGGACCCGAGAGTGTGGGTGTG
ACCATTGTGACCAGGNTGAGGCCTGAGCCTGTGTAGCTGTGGCGGCCTGTGTAGACCAGGCGGCCGTGAGGGTCTGT
ATGTGGCTTAGCTGGGTTAGTGTCTTCAACTCCGTCGGGCCGCCCCCTTCCCCACCGTGTTTTGGACCCCTGATGTG
TGTTGCCTATGCCCCGACAGGATGGTGACAGGTGTAGAGGATGGCGCCTGCCCTCCTCCAGACGCCAGGGTATTTGG
GTTTTCTGTGCCAGCCTGGTCCCCTGCTGAAGTGATCTCCAGTTGAGTGACCTCGCTTTGTCTCTAGGTCTCCATTT
CCTCAGTTGGGCCTTGCCCACCTCATAGGATCATACTGCATTTTGCAAACCATAAAGGCCCGCTTTGTAGTTATTTG
AGCATGCTGTTGTGTTGATCTAGATGGGTCCCACACGGGGGTGGATTCCGGARAAGGACAGGCGTGAGTCCCGCAAG
CTTGTGTGCATGGGGTCCGTTTCGTGTGTGTCTGTGCTGGTTGGGTGTGCCTTTGCACGGGCTGGGTTGTCAGGTTT
GCTCTGAGTGTGAGGGGCCAGGTGTGTGTATGCAGTTGGCCGGGTCTTCCGTTTCTCGGTGWCAGTTCGCTCCCTT
CAGCATTAGCCGCCCCAGCCTCCCTCCGCCCCCACAGACCCCGCCTGCTGGACCCAGGTGACTTACGCTCCTGGTGG
GGGCGGGGCGGGGCAGGGCGGCTTTGCCATCTTGGGGTGGGGGGCACTTGCCTGGGGCTGGACGTTGGGGGCGGGG
CAGGATTGAGATGGGGCCGGGGGTGGGGTCTGGATGGAGGTTGGCTGAGCTGGGCGGGGCATGGCTCAGGCATGGCT
GGGATAGATGGGGCTGGGCGGGCGAGGGGAGGGGCTGGGTGGGACGAGGGGAGGGTTTGGGCGGGCAAGGCTGGG
GCTGGGCGGATCTGAGTTGGTCCCCGAAGGCCCGGAGCTCTGACCCTCAGACGCCCCCTCTTGAACTGGCTTTTCCC
ACTCCTCCCTTTCTAAAACGAAGATGCGGCTGGGGGCCTTCCCCTCCAACGAGGGATCGAGGGCCGCGGGGCGAGCA
CTGAGTCGGATCCCTGGCTCTGGGGCCAGGCCAGGCCTTGGCCCGCTGATAGACCTCGAAGATGGCCATCATCTTTT
CTCCTTACCTCAGTGTCCTTGGCTCGGGCCCAGGGAACTGGCAGCCTGGTCTCCGGCATCGGATGGGACCGGGGGG
CGGGGAGGGGGTGAATGGGGCAGTGATTTGAAGAGGGGTCGCGGAGGCTGGGCATGAGGCGCGGCTGTCCTCACCGC
TCCCGCAGACAGCGTGGACGATGAATTTGAATTGTCCACCGTGTGTCACCGGCTGAGGGTCTGGAGCAGCTGCAGG
AGCAAACCAAATTCACGCGCAAGGAGTTGCAGGTCCTGTACCGGGGCTTCAAGAACGTGAGTGCNGGGCGAGGCCAA

FIGURE 22

ACTCAGCGNGGGTGGGACAGGAGGACCCAANCCGGTCCANATTTTTCCCANAAAGCATGGCTTNGATGCTTGAGGNG
CGGGCGGAAGGGAGGCAAGGCCCTGAGACTGAACTTCTAGCTGGAGGTTCTGGGGCGGGGCCAGAACGRAAGTGGCG
CCTGTAGACTGTCAGTTTCGTTCCATGTTTTTTATTTGTGCACTGGGAAAAGAAGTCTTCCCTCCCATCACATGAGCC
ACGTGGTGAGTCCTCTGGAGGCTTGAAGATTATCCCCCTCCCTGGGAGTCTTGGGCCATGGAGGGTGGGGGCGGTGA
ACGGAAGGGGATTTTGTCTCTGCCCTCAGCCTGGTGCCCTCTCCTTCCAGGAATGTCCCAGCGGAATTGTCAATGAG
GAGAACTTCAAGCAGATTTACTCCCAGTTCTTTCCTCAAGGAGGTGAGGGGACAAGGCCCAAGGGGAAGCAGTTGTC
CTTCTCTAGGCTGAGGGAGGGAGGGATTCTGGAGGAGCTGGGAATGCCAAGGTGATGGGGGGTATGGGGAGCTCCTT
AGAGGGAGGAAGTCCTCTCCTGTGTGGAAGCCAACTTCTCCACACTCACCCTGCAGACTCCAGCACCTATGCCACTT
TTCTCTTCAATGCCTTTGACACCAACCATGATGGCTCGGTCAGTTTGAGGTGAGCTGGCCGAGGTGGCCAGGGAA
GCCTGTTTCCTGGAGTTCAGGGCCAGGATCTCCAGGCCAAACCCAGAGAAGGAGTTGGGTGAAGAGKACCCGAGGAC
ACAGCTCCCTNCTGCCTTCTTCCCAGGACTTTGTGGCTGGTTTGYCCGTGATTCTTCGGGGAACTGTAGATGACAGG
CTTAATTGGGCCTTCAACCTGTATGACCTTAACAAGGACGGCTGCATCACCAAGGAGGTGCAGGGCAACTGAAGGGC
TGGGGGTCTGTGGCGGTGATGGGGGTGGCGTGCAKAGGGTGATGGGAGGGAAATATGACCCACATATGCCCACAAGC
AATGGGATCAAGGGAGGCTGGAGGCTCTGAGGAAGGATCCTCTTCTCTCTTGGCCTAACAGGAAATGCTTGACATCA
TGAAGTCCATCTATGACATGATGGGCAAGTACACGTACCCTGCACTCCGGGAGGAGGCCCCAAGGGAACACGTGGAG
AGCTTCTTCCAGGTACTTGGGAGTGGGTATGGCTGGAGGGCCCTGGAGTGAAGGGAAGAAGGCCAAGAACCAGCAGG
GAACTCACCTGACTTCTGTCTGCCTCTCTCTTGCCATCCCTCCTGTTCTCCCTGCCTGACCACCTTCTTGCAGAAGA
TGGACAGAAACAAGGATGGTGTGGTGACCATTGAGGAATTCATTGAGTCTTGTCAAAAGGTACAGCTCCCTGCCCTC
TACATTACCCTGACCTGGACTCAGGCCTGATTTAGTAATGCAGGGAAAAGCTTCTTTGGGAAGAATACCACCTTCCC
ACCTCACCCCCATATTTCAATCCTATTCCTTTGTGGGAGGCTTACCCCTTCCCTACCTCAGGTCTCTCTGGGCATCT
CCTTCCTCTGTGCTTTTGAATGTCCCCGTCTGTGACTCAAGTGTCCCTCTCACTGTCTCTGATAAAGCTCCTTCTCT
TTCTCTCTCTTCAATCTGCCTCGCTCACATCATGGCCACAGGATGAGAACATCATGAGGTCCATGCAGCTCTTTGAC
AATGTCATCTAGCCCCCAGGAGAGGGGGTCAGTGTTCCTGGGGGGACCATGCTCTAACCCTAGTCCAGGCGGACCT
CACCCTCTCTTCCCAGGTCTATCCTCATCCTACGCCTCCCTGGGGGCTGGAGGGATCCAAGAGCTTGGGGATTCAG
TAGTCCAGATCTCTGGAGCTGAAGGGGCCAGAGAGTGGGCAGAGTGCATCTCGGGGGGTGTTCCCAACTCCCACCAG
CTCTCACCCCCTTCCTGCCTGACACCCAGTGTTGAGAGTGCCCCTCCTGTAGGAATTGAGCGGTCCCCACCTCCTA
CCCCTACTCTAGAAACACACTAGACAGATGTCTCCTGCTATGGTGCTTCCCCATCCCTGACCTCATAAACATTTCC
CCTAAGACTCCCCTCTCAGAGAGAATGCTCCATTCTTGGCACTGGCTGGCTTCTCAGACCAGCCATTGAGAGCCCTG
TGGGAGGGGGACAAGAATGTATAGGGAGAAATCTTGGGCCTGAGTCAATGGATAGGTCCTAGRAGGTGGCTGGGGTT
GAGAATAGAAGGGCCTGGACAGATTATGATTGCTCAGGCATACCAGGTTATAGCTCCAAGTTCCACAGGTCTGCTAC
CACAGGCCATCAAAAATATAAGTTTCCAGGCTTTGCAGAAGACCTTGTCTCCTTAGAAATGCCCCAGAAATTTTCCAC
ACCCTCCTCGGTATCCATGGAGAGCCTGGGGCCAGATATCTGGCTCATCTCTGGCATTGCTTCCTCTCCTTCTTTCC
TGCATGTGTTGGTGGTGTTGGTGGGGGAATGTGGATGGGGGATGTCCTGGCTGATGCCTGCCAAAATTTCATCC
CACCCTCCTTGCTTATCGTCCCTGTTTTGAGGGCTATGACTTGAGTTTTTGTTTCCCATGTTCTCTATAGACTTGGG
ACCTTCCTGAACTTGGGCCTATCACTCCCCACAGTGGATGCCTTAGAAGGGAGAGGGAAGGAGGGAGGCAGGCATA
GCATCTGAACCCAGTGTGGGGGCATTCACTAGAATCTTCAATCAACCTGGGCTCTCCCCACCCCACCCCAGATAACC
TCCTCAGKTCCCTAGGGTCTCTTCTYGCTTGACTCAATCTACCCAGAGATGCCCCTTAGCACACCTAGAGGGCAGGG
ACCATAGGACCCAGGTTCCAACCCCATTGTCAGCACCCCAGCCATGCGGCCACCCCTTAGCACACCTGCTCGTCCCA
TTTAGCTTACCCTCCCTAGTTGGCCAGAATCTGAGGGGAGAGCCCCAGAGAGCCCCTTCCCATCAGAAGACTGTT
GACTGCTTTGCATTTTGGGCTCTTCTATATATTTTGTAAAGTAAGAAATATACCAGATC:TAATAAAACACAATGGC
TATGCACAGGCTGCCGTCTCTGCCTTTTGTCCCTCCCACCTACAAATACTACACACCCCTAACGAATGCACCTGCA
GCCTTTTAGATCCCCAAGAAAGTGGCTTTCTTTTCCATAGTTGGCCATACCTTGGCATGAGACTGAGACACAGGCTC
TGGAATGGTTGGAAACCCACCCAACCTCAGGCCCCCACATGAATCTCCCTCCCACACAGCCTGAGAGGAGACAAGGA
AGGAAGGACAGGACACTGATGTCCCGAAGACTGTGCCAAGCAAGCTGTTTTTAGCTGACATTCTTACAAGTTGAAT
CACAGATTTCTAATTTACAGACTTTTAGTTAATCTCAAAGTGCTTTCTTTTGAGGGGCCTCCTTTAAGTTCYTTCT
TTTTTTTTTTTTTT

FIGURE 22 (cont'd)

>monkey KChIP4 cds = 265 5

gtcgacccacgcgtccggtgcgctgtgg(gcgggggggagccccgccagccaaatgccaggatcagcatgagaggctgg
actttagtccaggtctgtcctcaccccgggggacgccggctttgcagggtgcagctgcgaggaactgctcactttttc
ccctgcaagtctttgttccaagcctgacgttgctacgattctgtaattaactccctccactccaaaggggtctggaggc
tgggatgctctgccagctcagaggaTGTTGACTCTGGAGTGGGAGTCCGAAGGACTGCAAACAGTGGGTA
TTGTTGTGAT
TATATGTGCATCTCTGAAGCTGCTTCATTTGCTGGGACTGATTGATTTTTCGGAAGACAGCGT
GGAAGATGAACTGGAGA
TGGCCACTGTCAGGCATCGGCCTGAGGCCCTTGAGCTTCTGGAAGCCCAGAGCAAATTTACC
AAGAAAGAGCTTCAGATC
CTTTACAGAGGATTTAAGAACGAATGCCCCAGTGGTGTTGTTAATGAAGAAACCTTCAAAGA
GATTTACTCGCAGTTCTT
TCCACAGGGAGACTCTACAACATATGCACATTTTCTGTTCAATGCGTTTGATACGGACCACA
ATGGAGCTGTGAGTTTCG
AGGATTTCATCAAAGGTCTTTCCATTTTGCTCCGGGGGACAGTACAAGAAAAACTCAATTGG
GCATTTAATCTGTATGAT
ATAAATAAAGATGGCTACATCACTAAAGAGGAAATGCTTGATATAATGAAAGCAATATACG
ACATGATGGGTAAATGTAC
ATATCCTGTCCTCAAAGAAGATGCACCCAGACAACACGTCGAAACATTTTTTCAGAAAATGG
ACAAAAATAAAGATGGGG
TTGTTACCATAGATGAGTTCATTGAAAGCTGCCAAAAAGATGAAAACATAATGCGCTCCATG
CAGCTCTTTGAAAATGTG
ATTTAActtgtcaactagatcctgaatccaacagacaaatgtgaactattctaccacccttaaagtcggagctaccactt
ttagcatagattgctcagcttgacactgaagcatattatgcaaacaagctttgttttaatataaagcaatccccaaaaga
tttgagtttctcagttatataatttgcatcctttccataatgccactgagttcatgggatgttctaactcatttcatactc
tgtgaatattcaaaagtaatagaatctggcatatagttttattgattccttagccatgggattattgaggctttcacata
tcagtgattttaaaatacctagtgttttttgctctcattttgtatgtattcagtcctaggattttgaatggttttctaatat
actgacatctgcatttaatttccagaaattaaattaattttcatgtctgaatgctgtaattccatttatatactttaagt
aaacaaataagattactacaattaaacacatagttccagtttctatggccttcccttcccacctctatttataaattaat
tttatctggtatttttaaacatttaaaaatttatcatcagatatcagcatatgcctaatttatgctcaatgaaacttaata
agcatttaatttttccatcatacattatagccaaggcctatatactatatataattttggatttgtttaatcttacaggct
gttttccattgtatcatcaagtggaagttcaagacggcatcaaacaaaacaaggatgtttacagacatatgcaaagggtc
aggatatctatcctccagtatatgttaatgcttaatataacaagtaatcctaacagcattaaaggccaaatctgtcctcttt
cccctgacttccttacagcatgtttatattacaagccattcagggacaaagaaaccttgactaccccactgtctactagg
aacaaacaaacagcaagcaaaattcactttgaaagcaccagtggttccattacattgacaactactaccaagattcagta
gaaaataagtgctcaacaactaatccagattacaatatgattttagtgcatcataaaattccaacaattcagattatttttt
aatcatctcagccacaactgtaaagttgccacattactaaagacacacacatcgtcctgttttgtagaaatatcacaaa
gaccaagaggctacagaaggaggaaatttgcaactgtctttgcaacaataaatcaggtatctattctggtgtagagatag
gatgttgaaagctgccctgctatcaccagtgtagaaattaagagtagtacaatacatgtacactgaaatttgccatcgcg
tgtttgtgtaaactcaatgtgcacattttgtatttcaaaaagaaaaaataaagcaaaataaaatgttwawaamwmwaaa
aaaaaaaaaaaa

>monkey KChIP4
MLTLEWESEGLQTVGIVVIICASLKLLHLLGLIDFSEDSVEDELEMATVRHRPEALELLEAQSKFT
KKELQILYRGFKNE
CPSGVVNEETFKEIYSQFFPQGDSTTYAHFLFNAFDTDHNGAVSFEDFIKGLSILLRGTVQEKLNW
AFNLYDINKDGYIT
KEEMLDIMKAIYDMMGKCTYPVLKEDAPRQHVETFFQKMDKNKDGVVTIDEFIESCQKDENIM
RSMQLFENVI

FIGURE 23

>monkey KChIP4 C terminal splice variant cds = 265-966

gtcgacccacgcgtccggtgcgctgtggttgcgggggggagccccgccagccaaatgccaggatcagcatgagaggctgg
actttagtccaggtctgtcctcaccccggggagaccgccggctttgcagggtgcagctgcgaggaactgctcactttttc
ccctttgcaagtctttgttccaagcctgacgttgctacgattctgtaattaactccctccactccaaaggggtctggaggc
tgggatgctctgccagctcagaggATGTTGACTCTGGAGTGGGAGTCCGAAGGACTGCAAACAGTGGGTA
TTGTTGTGAT
TATATGTGCATCTCTGAAGCTGCTTCATTTGCTGGGACTGATTGATTTTTCGGAAGACAGCGT
GGAAGATGAACTGGAGA
TGGCCACTGTCAGGCATCGGCCTGAGGCCCTTGAGCTTCTGGAAGCCCAGAGCAAATTTACC
AAGAAAGAGCTTCAGATC
CTTTACAGAGGATTTAAGAACGAATGCCCCAGTGGTGTTGTTAATGAAGAAACCTTCAAAGA
GATTTACTCGCAGTTCTT
TCCACAGGGAGACTCTACAACATATGCACATTTTCTGTTCAATGCGTTTGATACGGACCACA
ATGGAGCTGTGAGTTTCG
AGGATTTCATCAAAGGTCTTTCCATTTTGCTCCGGGGGACAGTACAAGAAAAACTCAATTGG
GCATTTAATCTGTATGAT
ATAAATAAAGATGGCTACATCACTAAAGAGGAAATGCTTGATATAATGAAAGCAATATACG
ACATGATGGGTAAATGTAC
ATATCCTGTCCTCAAAGAAGATGCACCCAGACAACACGTCGAAACATTTTTTCAGGCTGTTT
TCCATTGTATCATCAAGT
GGAAGTTCAAGACGGCATCAAACAAAACAAGGATGTTTACAGACATATGCAAAGGGTCAGG
ATATCTATCCTCCAGTATA
TGTTAAtgcttaataacaagtaatcctaacagcattaaaggccaaatctgtcctctttccccgacttccttacagcatg
tttatattacaagccattcagggacaaagaaaccttgactaccccactgtctactaggaacaaacaaacagcaagcaaaa
ttcactttgaaagcaccagtggttccattacattgacaactactaccaagattcagtagaaaaataagtgctcaacaacta
atccagattacaatatgatttagtgcatcataaaattccaacaattcagattatttttaatcatctcagccacaactgta
aagttgccacattactaaagacacacacatcgtccctgttttgtagaaatatcacaaagaccaagaggctacagaaggag
gaaatttgcaactgtctttgcaacaataaatcaggtatctattctggtgtagagataggatgttgaaagctgccctgcta
tcaccagtgtagaaattaagagtagtacaatacatgtacactgaaatttgccatcgcgtgtttgtgtaaactcaatgtgc
acattttgtatttcaaaaagaaaaaataaaagcaaaataaaatgttwawaamwmwaaaaaaaaaaaaaaa

>monkey KChIP4 C terminal splice variant

MLTLEWESEGLQTVGIVVIICASLKLLHLLGLIDFSEDSVEDELEMATVRHRPEALELLEAQSKFT
KKELQILYRGFKNE
CPSGVVNEETFKEIYSQFFPQGDSTTYAHFLFNAFDTDHNGAVSFEDFIKGLSILLRGTVQEKLNW
AFNLYDINKDGYIT
KEEMLDIMKAIYDMMGKCTYPVLKEDAPRQHVETFFQAVFHCIIKWKFKTASNKTRMFTDICK
GSGYLSSSIC

FIGURE 24

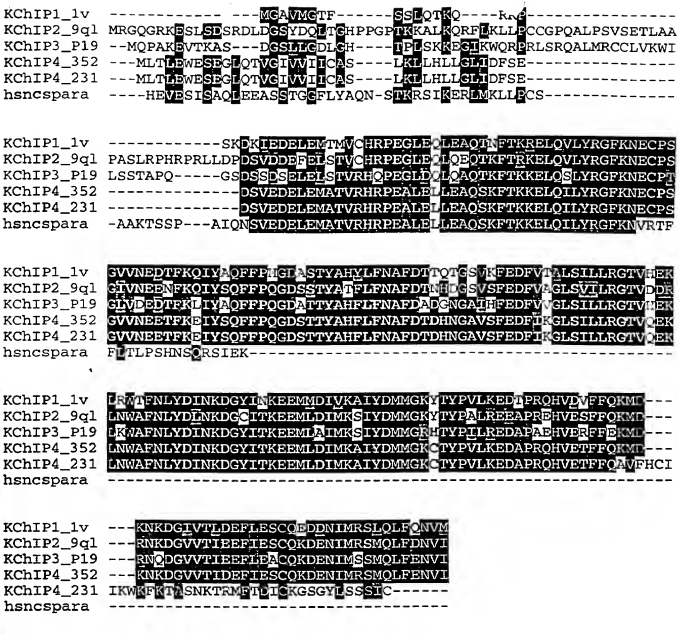
KChIP1_1v
KChIP2_9ql
KChIP3_P19
KChIP4_352
KChIP4_231
hsncspara

FIGURE 25

Rat 33b07 protein
MNGVEGNNELPLANTSTSALVPEDLDLKQDQPLSEETDTVREMEAAGEAGAEGGASPDSEHCDPQLCLRVAENGCAAAAG
EGLEDGLSSSKCGDAPLASVAANDSNKNGCQLAGPLSPAKPKTLEASGAVGLGSQMMPGPKKTKVMTTKGAISATTGKEG
EAGAAMQEKKGVQKEKKAAGGGKDETRPRAPKINNCMDSLEAIDQELSNVNAQADRAFLQLERKFGRMRRLHMQRRSFII
QNIPGFWVTAFRNHPQLSPMISGQDEDMMRYMINLEVEELKHPRAGCKFKFIFQSNPYFRNEGLVKEYERRSSGRVVSLS
TPIRWHRGQEPQAHIHRNREGNTIPSFFNWFSDHSLLEFDRIAEIIKGELWSNPLQYYLMGDGPRRGVRVPPRQPVESPR
SFRFQSG.

Rat 33b07 DNA (coding: 85-1308)
GGTGGAGCTAAGCACTCACTGCGGTGCTGCCCTGCGTCTGCAGAGAACAAGGAAAGCTTCTCTGCAGGGCTGTCAGCTGC
CAAAATGAACGGCGTGGAAGGGAACAACGAGCTCCCTCTCGCTAACACCTCGACCTCCGCCCTTGTCCCGGAAGATCTGG
ATCTGAAGCAAGACCAGCCGCTCAGCGAGGAAACTGACACGGTGCGGGAGATGGAGGCTGCAGGTGAGGCCGGTGCGGAG
GGAGGCGCGTCCCCCGATTCGGAGCACTGCGACCCCCAGCTCTGCCTCCGAGTGGCTGAGAATGGCTGTGCTGCCGCAGC
GGGAGAGGGGCTGGAGGATGGTCTGTCTTCATCAAAGTGTGGGGACGCACCCTTGGCGTCTGTGGCAGCCAACGACAGCA
ATAAAAATGGCTGTCAGCTTGCAGGGCCGCTCAGCCCTGCTAAGCCAAAAACTCTGGAAGCCAGTGGTGCAGTGGGCCTG
GGGTCGCAGATGATGCCAGGGCCGAAGAAGACCAAGGTAATGACTACCAAGGGCGCCATCTCTGCGACTACAGGCAAGGA
AGGAGAAGCAGGGGCGGCAATGCAGGAAAAGAAGGGGGTGCAGAAAGAAAAAAAGGCAGCTGGAGGAGGGAAAGACGAGA
CTCGTCCTAGAGCCCCTAAGATCAATAACTGCATGGACTCCCTGGAAGCCATCGATCAAGAGCTGTCAAATGTAAATGCG
CAAGCTGACAGGGCCTTCCTCCAGCTGGAACGCAAATTTGGGCGGATGAGAAGGCTCCACATGCAGCGCCGAAGTTTCAT
CATCCAAAACATCCCAGGTTTCTGGGTCACAGCGTTTCGGAACCACCCGCAACTGTCACCGATGATCAGTGGCCAAGATG
AAGACATGATGAGGTACATGATCAATTTAGAGGTGGAGGAGCTTAAGCACCCAAGAGCAGGGTGCAAATTTAAGTTCATC
TTCCAAAGCAACCCCTACTTCCGAAATGAGGGGCTGGTCAAAGAGTACGAGCGCAGATCCTCAGGTCGAGTGGTGTCGCT
CTCTACGCCAATCCGCTGGCACCGGGGTCAAGAACCCCAGGCCCATATCCACAGGAATAGAGAGGGGAACACGATTCCCA
GTTTCTTCAATTGGTTCTCAGACCACAGCCTCCTAGAATTCGACAGAATAGCTGAAATTATCAAAGGGGAGCTTTGGTCC
AATCCCCTACAATACTACCTGATGGGCGATGGGCCACGCAGAGGAGTTCGAGTCCCACCAAGGCAGCCAGTGGAGAGTCC
CAGGTCCTTCAGGTTCCAGTCTGGCTAAGCTCTGCCCTCGTGAGAAGCTCTTACAGAAGAGTCCTTACCACCTTCTCAGC
TTGGCTAGCAGCATGCAGCCTTCTGTCTGCTTTCTCTTCCTTGGATTGTGTCCTTTGGTTCTTCTAAGTCTCCGGTAGTT
TCAAGGTTGTGGCTTCCAAGTCTTTGCTCTTCTTTCTCTTGGCCATCACGATGTCCTGCATAGTGTTAATGGTGTTCCAA
GTGCATGGCCTCCAAACTGCTTCTATGCCAAGCTCACGTGCTGTAGTTTGTACTGCTTTTCTTTGCATGGCTTGGTTCCT
GTCTGTGATCTTCTAGGTTTTTTGTTTTCTTTTTTAAAAGTGGTTCTCTATCAAAAGAAAGCTTGACATATCCTTACCAA
GAACTAGCCAGATTTCATACTGTGTTCCCGATATCTATGTACTGTGAAGAACTGTGAGTTTCGCCACTGCAAGATGGGAC
TGTATCCCAATCCAGCCATCAGCCCAACAGGACATTCCAAGCTGTCACCAACTGATCCTAGCTGTCTTCCTGGGCCTTTG
CCATTTACCCTGCTTTTTATCTATAGAATGAGCAGGTGGCTGGTAGGTGACTACTAGGTAAGAGTGAAGTATTAGGTGAG
GAGTGTTTTCTGTCACCACATTGTTCTTGTACCAATGCATCATGATCAGCTTGGATCAGCTACTGACTGTCTGATATTTC
TAACCCCCAACACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 26

Human 33b7 (106d5) DNA (coding: 88-1332)

GGGGTGGTGCTAGACGTTTCGGGCAGAGCTCGGCCGCTGCGGAGGACAAGGAACTCTCCCTCTCCCACTAGTCTGACTTC
TTCCAAAATGAGCGGCCTGGATGGGGGCAACAAGCTCCCTCTCGCCCAAACCGGCGGCCTGGCTGCTCCCGACCATGCCT
CAGGAGATCCGGACCTAGACCAGTGCCAAGGGCTCCGTGAAGAAACCGAGGCGACACAGGTGATGGCGAACACAGGTGGG
GGCAGCCTGGAGACCGTTGCGGAGGGGGGTGCATCCCAGGATCCTGTCGACTGTGGCCCCGGCGCTCCGCGTCCCAGTTGC
CGGGAGTCGCGGCGGTGCAGCGACCAAAGCCGGGCAGGAGGATGCTCCACCTTCTCAGAAAGGTCTGGAAGCAGCCTCTG
CCGCCGAGGCTGCTGACAGCAGCCAGAAAAATGGCTGTCAGCTTGGAGAGCCCCGTGGCCCTGCTGGGCAGAAGGCTCTA
GAAGCCTGTGGCGCAGGGGGCTTGGGGTCTCAGATGATACCGGGGAAGAAGGCCAAGGAAGTGACGACTAAAAAACGCGC
CATCTCGGCAGCAGTGGAAAAGGAGGGAGAAGCAGGGGCGGCGATGGAGGAAAAGAAGGTAGTGCAGAAGGAAAAAAAGG
TGGCAGGAGGGGTGAAAGAGGAGACACGGCCCAGGGCCCCGAAGATCAATAACTGCATGGACTCACTGGAGGCCATCGAT
CAAGAGTTGTCAAACGTAAATGCCCAGGCTGACACGGGCCTTCCTTCAGCTTGAGCGCAAGTTTGGCCGCATGCGAAGGCT
CCACATGCAGCGCAGAAGTTTCATTATCCAGAATATCCCAGGTTTCTGGGTTACTGCCTTTCGAAACCACCCCCAGCTGT
CACCTATGATCAGTGGCCAAGATGAAGACATGCTGAGGTACATGATCAATTTGGAGGTGGAGGAGCTTAAACACCCCAGA
GCAGGCTGCAAATTCAAGTTCATCTTTCAGGGCAACCCCTACTTCCGAAATGAGGGGCTTGTCAAGGAATATGAACGCAG
ATCCTCTGGCCGGGTGGTGTCTCTTTCCACTCCAATCCGCTGGCACCGAGGCCAAGACCCCAGGCTCATATCCACAGAA
ACCGGGAAGGAACACTATCCCTAGTTTCTTCAACTGGTTTTCAGACCACAGCCTTCTAGAATTCGACAGAATTGCAGAG
ATTATCAAAGGAGAACTGTGGCCCAATCCCCTACAATACTACCTGATGGGTGAAGGGCCCCGTAGAGGAATTCGAGGCCC
ACCAAGGCAGCCAGTGGAGAGCGCCAGATCCTTCAGGTTCCAGTCTGGCTAATCTCTGTCCTGTGAGAAGCTTCTGCACA
AGTTTCCTTACCACCTCCTCTTGGACCTATGCTTGGCCAACAGCATGCAGTCTTCCATCTGCTTTCTCTTCATACTGTGG
ATTATCTTTTCCTTTGGTTCTAAATCTTCAGTAATCGGTTGCAAGATTGTTGGCTTACCTGCCTGTGCCATTCTTCCTCT
GGGCCTTCATGCTTTTCTGCATTGTGTTAACATGTTTCAAGTGCATGGCCTTCTACGGCTTCTATGCCAAGCGTATGATA
CTATAGATATAGTGTACCATACTGCCTTTCTTTGCATGGCTTGGACCCTATCTGTGACCATGCTCTTCTCCCAATTTAAG
TGGTTCTGTACCACAAAGAATCTTGATACATTTTCACAAATAACTGATTGGGCTTCATACTTTATGCTGGCTGTGTCCTG
ATACCCATGTACTTATGGTAAGCTATTTGGGTATTACCACTGCAAGACAAAACTGATATCTTAACCCGGCCATCAACCCA
AATTGGACATTCCAGACTACCACCAACTGGATCCCAGCTGCCTTCCTGGGCTTGTGCCATCCACCCTACTGGTTATCTGA
TAGAACAAGCTGGTGGCTGATGGGTGACTGCTAGGCGTGACTGAGGTAATAGATGAAAAGTGTTCTATGTTATCACATTG
GTTTTCCTGTACCTTTGGTTACTCTACGTCATGACCCAGCTGCTGGTGAGTATGAAGCCTGTGCTATAGCCCCACCCCTACT
CACTCTCACCTTCTGGTTGAACTTTGCTTAGGCCACCATTGTCTGCCTCATCAGGAACTATCTGTAGACGTAGCTCCCAG
GGAGCTCACAGCAACACCCCCTACCACCCAGGATGGGCAGTAATATGTGACAGAGCCCAAAGCAAGGCTGGAACGCAGTCC
CTTCCAGCTTAGTCTTTCTGACTCCTAGCCAACAAACCATCCTTAATGTGAGCAACTTCTTTAGGCATTTCCTCTTTTCC
CCGCCTGCACCCACTCTGAACATGACAAAAGTTGCCAGAGTTGGGGCATTGAGGAAGAGATATTTCTGGAATGTGAGACT
TGTTATGCCTCTGTCTCTTTCTCTCCCTCCCCCTCCCCTCTCCCTCCCCCTCTCCCTCCCATCCCTTTCTTCCCTTTCA
CTCTGAAGCAGTTTTAGCTATTAACAGAAAACAAAACTGGCAAAGCAGGCTTTTTGTTTAATTTGCTCTTTCCCTGATT
GTGTTCAGAGAGAAAGGTTATGATTAAATGGGCTCCAGATCTCTTATTGCCTTTATTCCTCCACCCCACTTCTTTTAGCA
AGGTCTGAAAGTTCAAAGGGAGACCTATAGGTTAATTGTTTAGTTATAGGCAGTGTTAAATTAAGTAGGCAGATTTTGACATA
TTTATCTTTTTACCCCATCCATTCTACCAAAACCTGTGTATTTCTTGAGTTTTTAGTTTGAGAAGCTGGAAAGAGAGAGA
AGGGCCTCACAGTGATGGGTTCAGGACGGGTCAAAGGCAAAGGCCTTTGTGATGTGAGCAAAGGCAACCAAAACTTAGCC
TCACTCCACTTTTCTAAAGATGGAAATTCTTTTTTGGGCCTTGGACTGCTTCTAGGGTAGCATTTTGTAGGTCACTCTTC
TCCTTTGTACTATTTTGTTTCTGCCCTGATGTCCCTTGGGTCTCCATCCTACTGCCTGGCTTTCTTGGCCCTCATTTCTC
AGCTTCTGCATTTCCTTCCCTGCTCCCTAACAAATGAAGAAGCAGGCTGCAGCCTGCATTGTGGAAGATCTCCAGCCTCCT
TGTAGGGGATAAGGGGATGTGTAGCATCTGTGTGGATTTTCACGGACAAGTTCCAGTAGGTGGGACAGTGATGCCGTCAA
GGCTTAGTTATGATCATGTGTGGTGATAAAGACCATCCACCATCACCCTTTTCCCCTTTGGTTTTGAAGGCCTTGCCCTA
AGCTACCTGAGGGTTTAGGAGGTCTGAACACACACAGTGGAGAGGTTAATCTAGGTTGGGAAACTGATGCAAAGTCCAGA
GCAGGAATGAGCCTGCTGTGGCGTGGGTTTGGAAAGGCTCACAGGAAAGAACCTGCAGGATCAGGGGTGGGAGGGGAGGC
CCCTGAGGTGCTCTCCAGGGAAGAGGGGCTGGGGTTTAAATAGCATGCTTGAGGAAGATTTCCTCAATTTTTCCTAA
GTCCTTGAATTCACCAGTAGATTTTTGTAAACAAAATGTAAGTCGATGTTTCTCTCAATTATCCTAGGAGTGACCTTTA
TATGTGTGGAAGATTAATGGTATATGCTCCTATGTCACTGTTTTGAGTAAAATCCATTTCCTTTCTCTGTTTCAGCCT
ATGACAAAATTGATGTTTACAGGCCTGCTTTTTGCTTATAATTGACAACATGTGCAAAAATACCAAATTTGTGTCCTGTG
CAGTATGAAGAATTCAGTGAATATTCATTAATGATTAGCTTGTTTTGCTCTCTGTTCATATATGGCTCTATTCTTAGAA
ATATAATTTGAATGTGATCTTTCAATAGTCTGAATATTTTACAAATTATAGCTATGTCTTGTGAAAATAACCTCAAAAAG
AAAAATACGACTCTGTTGTTTACTTGATATTTCTTGCCCTAGTAATGTACTTGACATTTATGTTCCTAAGCAGTGTAAG
TACCAGTAGAATTCTCTGTCAAACTCAATGATCATTTAGTACTTTTGTCTTCTCCCATGTGCTTGAAGGAAAATAAAG
TGTCACTACCGTATTTCTTGTTTTCATCAAAAAATAAAAATAATTTAAAAAACAAAAAAAAAAAAAA

Human 33b7 (106d5) protein

MSGLDGGNKLPLAQTGGLAAPDHASGDPDLDQCQGLREETEATQVMANTGGGSLETVAEGGASQDPVDCGPALRVPVAGS
RGGAATKAGQEDAPPSTKGLEAASAAEAADSSQKNGCQLGEPRGPAGQKALEACGAGGLGSQMIPGKKAKEVTTKKRAIS
AAVEKEGEAGAAMEEKKVVQKEKKVAGGVKEETRPRAPKINNCMDSLEAIDQELSNVNAQADRAFLQLERKFGRMRRLHM
QRRSFIIQNIPGFWVTAFRNHPQLSPMISGQDEDMLRYMINLEVEELKHPRAGCKFKFIPQGNPYFRNEGLVKEYERRSS
GRVVSLSTPIRWHRGQDPQAHIHRNREGNTIPSFFNWFSDHSLLEFDRIAEIIKGELWPNPLQYYLMGEGPRRGIRGPPR
QPVESARSFRFQSG

FIGURE 27

Rat lp protein (partial)

LKGARPRVVNSTCSDFNHGSALHIAASNLCLGAAKCLLEHGANPALRNRKGQVPAEVVPDPMDMSLDKAEAALVAKELRT
LLEEAVPLSCTLPKVTLPNYDNVPGNLMLSALGLRLGDRVLLDGQKTGTLRFCGTTEFASGQWVGVELDEPEGKNDGSVG
GVRYFICPPKQGLFASVSKVSKAVDAPPSSVTSTPRTPRMDFSRVTGKGRREHKGKKKSPSSPSLGSLQQREGAKAEVGD
QVLVAGQNRDCAFLWEDRLCSRLLVWH

Rat lp DNA (partial, coding:1-804)

CTGAAAGGGGCGAGGCCCAGGGTGGTGAACTCCACCTGCAGTGACTTCAACCATGGCTCAGCTCTGCACATCGCTGCCTC
GAATCTGTGCCTGGGCGCCGCCAAATGTTTACTGGAGCATGGTGCCAACCCAGCGCTGAGGAATCGAAAAGGACAGGTAC
CAGCGGAAGTGGTCCCAGACCCCATGGACATGTCCCTTGACAAGGCAGAGGCAGCCCTGGTGGCCAAGGAATTGCGGACG
CTGCTAGAAGAGGCTGTGCCACTGTCCTGCACCCTTCCTAAAGTCACACTACCCAACTATGACAACGTCCCAGGCAATCT
CATGCTCAGCGCGCTGGGCCTGCGTCTAGGAGACCGAGTGCTCCTCGATGGCCAGAAGACGGGCACGCTGAGGTTCTGCG
GGACCACCGAGTTCGCCAGTGGCCAGTGGGTGGGCGTGGAGCTAGATGAACCGGAAGGCAAGAACGACGGCAGCGTTGGG
GGTGTCCGGTACTTCATCTGCCCTCCCAAGCAGGGTCTCTTTGCATCTGTGTCCAAGGTCTCCAAGGCAGTGGATGCACC
CCCCTCATCTGTTACCTCCACGCCCCGCACTCCCCGGATGGACTTCTCCCGTGTAACGGGCAAAGGCCGGAGGGAACACA
AAGGGAAGAAGAAGTCCCCATCTTCCCCATCTCTGGGCAGCCTGCAGCAGCGTGAAGGGGCCAAAGCTGAAGTTGGAGAC
CAAGTCCTTGTGGCAGGCCAGAACAGGGATTGTGCGTTTCTATGGGAAGACAGACTTTGCTCCAGGTTACTGGTATGGCA
TTGAACTGGACCAGCCCACGGGCAAGCATGACGGCTCTGTGTTCGGTGTCCGGTACTTTACCTGTGCCCCGAGGCACGGG
GTCTTTGCACCAGCATCTCGTATCCAGAGGATTGGTGGATCCACTGATCCCCCTGGAGACAGTGTTGGAGCAAAAAAAGT
GCATCAAGTGACAATGACACAGCCCAAACGCACCTTCACAACAGTCCGGACCCCAAAGGACATTGCATCAGAGAACTCTA
TCTCCAGGTTACTCTTCTGCTGCTGGTTTCCTTGGATGCTGAGGGCGGAGATGCAGTCTTAGAGACCTGGATACCTGACA
CAGAGACAGAGTCCCCTCTAGCATCTCCTGACACAAGGAGACCCCAGTCACCCTAAGATAGAGATTCCCAGTGACACCTC
CAGAATAGAAACCCCGTTAGCCAGCCCTCGATTACTGAGGTCCCATTATTAACAGATCTCCCATGACGACTCCCCCAAAT
ACAGACCTCATGTTACCCCAAAAGAGATTCCCTGAGTAGCACCTTCAGGCTAGTCCCTGTCCCCTACCCCTCAGAGCAGA
TTTCCCCCAATAAACATTTTCCACATCACCCAAGGGATGCTGACCCTCTCCACGACAGGACGTTCTTGAGTTACCAGTGG
ATTAGAGTCCCATGAATGAAGACCCCCCCCACCCCGGTTCTCCTTAAGCATAGGTCATACCTCCAGAATAGCCAGCCACA
TCACTATCCCCATGTAACATCAGTCTCCTCAAAATGGCGTGAGGTCACTAGAAAGACCTTATACTCTCCTCTCCTTCTCA
GAGATGCCCTCCATTCACTTAAGTCCCTGTTCTCACCCCTGAACAAGACACCTAATTAACCGGCCCACTCACCTCAATTA
CAAACACCAAAATCGTCCTGGAAGCATGAATTACAGGACAGCAAGTCTTCCTGCCCTCTGCACCCTTGAGAAACCCCCAG
TGCCTTGTATGAAGCCCACCCCACATGGCCCACAGTCCCTGTGCTGGCCAAGGCTCCCAGAAAATTCTCTATTTTTTAAA
GTAATAACTTCCCCCCCTTTGGGGGGATCCCCAAATTTGGAGACCCCATTCTAGAACACTGGGGAGTTCAAATTCCAGAG
AGAATATATATTATATATAATCCCCAATTCCCCATGCTTCCAAGCCCTACAATCTCTAGAAGACCCCAAATTTCTAATTC
CCAGGACTTCCCCTACCCAAGTCACAGAATCTTCAAATCCCCAGGGAATCCCAAACTTAAGATACCAATCCCAAACCCTC
AGGAAATCCCCCAACACAAGTCCTTAGGACCGGGAGGAAGGAACCTGTTGCCAGGAGAACATCCCAGGCTCTCAGGGCA
TCTCAAACCTGACTCCCAGGCACCAGGAGACCCCAAACAGAAAGTCCCATCTTTGGAACAAGGATAGGACTCTAATACCC
TTAGTCCATGGATCTTTAATTTCCAACCTCCAAACTCCATGGGCCCCACCCTCAAGGGAACCCCCAAGATCCAAATCTC
TGATAACTAATATGTGCAGGGCCCCAGGGCTCTAACAGGACCCCAAATCATGGAGTCCCTACTTCAATCTACCTTCTGGT
CACAGGTCCAAGACACTAAATCTGAGTCATTGGCCCCAAAGGACTTCACAGCACCTGGGCCAGACTAACAGCCTGAGGGA
GAACCTGAGGGCCCCGTGGGTCCAGAGCAGACCTGGGGCCCTGACCACCAAGGACAGCTCACGACTGCCCCTTCACTGCA
TGTCCCTAAACTCAGCATGACTCCTGTCCTCTTCAATAAAGACGTTTCTATGGCAAAAAAAAAAAAAAAAAAAAAAAAA
AAA

FIGURE 28

Rat 7s Protein (partial)
ADSTSRWAEALREISGRLAEMPADSGYPAYLGARLASFYERAGRVKCLGNPEREGSVSIVGAVSPPGGDFSDPVTSATLG
IVQVFWGLDKKLAQRKHFPSVNWLISYSKYMRALDEYYDKHFTEFVPLRTKAKEILQEEEDLAEIVQLVGKASLAETDKI
TLEVAKLIKDDFLQQNGYTPYDRFCPFYKTVGMLSNMISFYDMARRAVETTAQSDNKITWSIIREHMGEILYKLSSMKFK
DPVKDGEAKIKADYAQLLEDMQNAFRSLED

Rat 7s DNA (partial, coding: 1-813)

GCTGACTCTACCTCTAGATGGGCTGAGGCCCTCAGAGAAATCTCTGGTCGCTTAGCTGAAATGCCTGCAGATAGTGGATA
CCCTGCATACCTTGGTGCCCGACTGGCTTCTTTCTATGAGCGAGCAGGCAGAGTGAAATGTCTTGGAAACCCTGAGAGAG
AAGGGAGTGTCAGCATTGTAGGAGCAGTTTCTCCACCTGGTGGTGATTTTTCTGATCCAGTCACATCTGCTACTCTGGGT
ATTGTTCAGGTGTTCTGGGGCTTGGATAAGAAGCTAGCTCAGCGCAAGCACTTCCCGTCCGTCAACTGGCTCATTAGCTA
CAGCAAGTACATGCGCGCCCTGGACGAGTACTATGACAAACACTTCACAGAGTTCGTGCCTCTGAGGACCAAAGCTAAGG
AGATTCTGCAGGAAGAGGAGGATCTGGCGGAAATCGTGCAGCTCGTGGGAAAGGCGTCTTTAGCAGAGACAGATAAAATC
ACCCTGGAGGTAGCAAAACTTATCAAAGATGACTTCCTACAACAAAATGGGTACACTCCTTATGACAGGTTCTGTCCATT
CTATAAGACGGTGGGGATGCTGTCCAACATGATTTCATTCTATGATATGGCCCGCCGGGCTGTGGAGACCACCGCCCAGA
GTGACAATAAGATCACATGGTCCATTATCCGTGAGCACATGGGGGAGATTCTCTATAAACTTTCCTCCATGAAATTCAAG
GATCCAGTGAAGGATGGCGAGGCAAAGATCAAGGCCGACTACGCACAGCTTCTTGAAGATATGCAGAACGCATTCCGTAG
CCTGGAAGATTAGAACTGTGACTTCTCTCCTCCTCTTCCGCAGCTCATATGTGTATATTTTCCTGAATTTCTCATCTCCA
ACCCTTTGCTTCCATATTGTGCAGCTTTGAGACTAGTGCCTCGTGCGTTCTCGTTCATTTTGCTGTTTCTTTGGTAGGTC
TTATAAAACACACATTCCTGTGCTCCGCTGTCTGAAGGAGCTCCTGACCTTTGTCTGAAGTGGTGAATGTAGTGCATATG
ATACACAGTGTAACATACACATTGTAACATATACGTTCTGTAAACTTGTATGTAAGGTGACTACCCCTTCCCTCCTCTCC
AGTAAACTGTAAACAGGACTACTGCATGTGCTCTATTGGGGATGGAAGGCCAGATCTCCATACCGTGGACAGGTACATAA
GGAAACTAGACCACTTGCAACTTAGTGTTTGTTGAGTAACCATTTTGCAGGAAGTATTTCCATTTAAAAAACAAAAGATT
AATGTTCCAATTATTTGTAGCTTCCCCAGTATCAATCAGGACTGTTTGTGGCGCACTTGGGAACTATTTTGTTTTCCTAA
CAGACGTTTGCAAGGCTGAACGTAATAGATAAATCAGTTCCCTCTGAAAGTGTGAAAGTAAAAAGAGAGCTAGGTGGTCA
GACTTAAATTGACATCGTCTTGTTTAAGCATATTTTATTTCACTGAGAGATTTAATATCAAGGACTTTTATATACTCAAT
TACTAGGAAATCTTTTTTTAAGTACAATTTAAAAATCATTGAAAATGTGATCCACATCATAGCCATTTTCCTTATATTTA
GTCAGATGAGCTCAGAGTGGGGAGGGTGTGGGTTAGAATACCACAAGGACACGCAGCAGTGCCTGCAGGCAGTGTGGCCG
GGGGCCAGAGCGGCATTGTTTTCACGAGGTACGTGTGTGGCGTGTGTGTTTGCTTGTTGACACTCTGAAAACAGCAAGCT
TACCAGTTCCAGGAAATATTTTGTTTTCTTTCACTGGCTCAGAAAGCTCCTCAAAGTACCTGGTCCCTGAAGCTTCCTAT
CTGTTAATAGAGACGAGAGAGGTTCTTAAATTTAACTGGTGACAAAACAAAAAGAAAAAAAAAGATCGATTTTTGTCTTGC
TGTTTTGGTGTGTTTAAATAATAATTCCATATTTGCATAACGAGGCTCGCTTCTGAGAGCTTGGAGATCGTGCTCCCTCT
TCACTCTCCGGGGTGATAATGCTGGCGCCATGCTACCTCTTCAGGAGGGGAAGGGGATTGAACATGGCTAACACTCTCAA
GTACACAAGCGTAACGACAAAGTATTTATTTTAAGCCTTGGTATGTTGTTTAAATTATTAGGTGGTGCATTTCTTATGGT
CTTTTGGGTAGACATAGTATACACTTCAGATGTAATGTGTAAATCCTTGCTAGTGCATGTCTACACGATAGACTGCTATT
CAAGAAGGATATTCTTCCACATAACAATTTAAAAACTATTAAATCAGATATGGATTATGCAATGACTTGTTGAGAGGTGG
ATTAACGGTGCTGCTTAATCAGTTTGCTTCCAATATGGCTTCGTATCCAGAAGCCCTGACTAGTGGAGATGAGAAAGATT
TCAAAACCTGTCTGCCTACACCTACCAGCAACCTAGGCTTGTGATCAGAATGAATGATCCCAAGAAACTACTTGACCAAG
TGTGTTTTGTTGTCCTGGATTTGAGATGTGCGTTCTTCCTCCCTCTGAGACTGTTGATGTATGAGTGTGAAGAAGTTACA
GAAACAACGCTCAGATTTTCACGGTAACTTTCCCTCTGCCCACACTGTAGAGTTTCAGATTGTTCACTGATAGTGCTTCT
TTCGTAAGGATGTGTTAAAATATAGCAGTCTTTTTAAAAGATTATGCAGTTCTCTATTTATTGTGCTGTGCCTGGTCCTA
AGTGCAGCCGGTTAAACAAGTTTCATATGTATTTTTCCAGTGTTAAATCTCATACCTATGCCCTTTGGAAAGCTCCATCC
TGAACAATGAATAGAAGAGGCTATATAAATTGCCTCCTTATCCTTAAGATTTCACTATCTTTATGTTAAGAGTAATGTAT
AATTATTAAAATCTATGAAAAATAAAAAGTGGATTTAAATTAAGAGATC

FIGURE 29

Rat 29x protein

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ARLPAPEHARQQPLLSGPEPGSSARVPVPGVASRRQPRGGKPPSGDGLESGPSPRPLLHARGEAGLHRQSGRVPHTGTAY
FADEPTEAQAPGGFCVSPSLLGVRWPACATRTPGSLPLSPPSAQPRTLWPTPPAGPSSRMVARNQVAADNAISPASEPRR
RPEPSSSSSSSSPAAPARPRPCPVVPAPAPGDTHFRTFRSHSDYRRITRTSALLDACGFYWGPLSVHGAHERLRAEPVGT
FLVRDSRQRNCFFALSVKMASGPTSIRVHFQAGRFHLDGSRETFDCLFELLEHYVAAPRRMLGAPLRQRRVRPLQELCRQ
RIVAAVGRENLARIPLNPVLRDYLSSFPFQI
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Rat 29x DNA (coding: 433-1071)

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GCACGGCTCCCGGCCCCGGAGCATGCGCGACAGCAGCCCCTCCTCtCCGGCCCTGAGCCCGGATCGTCCGCCCGGGTTCC
AGTTCCCGGCGTGGCCAGTAGGCGGCAGCCGCGAGGCGGCAAGCCACCCAGCGGGGACGGCCTGGAGTCGGGCCCCTCTC
CACGCCCCCTTCTCCACGCGCGCGGGGAGGCAGGGCTCCACCGCCAGTCTGGAAGGGTTCCACATACAGGAACGGCCTAC
TTCGCAGATGAGCCCACCGAGGCTCAGGCTCCGGGCGGATTCTGCGTGTCACCCTCGCTCCTTGGGGTCCGCTGGCCGGC
CTGTGCCACCCGGACGCCCGGCTCACTGCCTCTGTCTCCCCCATCAGCGCAGCCCCGGACGCTATGGCCCACCCCTCCAG
CTGGCCCCTCGAGTAGGATGGTAGCACGTAACCAGGTGGCAGCCGACAATGCGATCTCCCCGGCATCAGAGCCCCGACGG
CGGCCAGAGCCATCCTCGTCCTCGTCTTCGTCCTCGCCGGCGGCCCCGGCGCGTCCCCGGCCCTGCCCGGTGGTCCCGGC
CCCGGCTCCGGGCGACACTCACTTCCGCACCTTCCGCTCCCACTCTGATTACCGGCGCATCACGCGGACCAGCGCTCTCC
TGGACGCCTGCGGCTTCTACTGGGGACCCCTGAGCGTGCATGGGGCGCACGAACGGCTGCGTGCCGAGCCCGTGGGCACC
TTCTTGGTGCGCGACAGTCGCCAGCGGAACTGCTTCTTCGCGCTCAGCGTGAAGATGGCTTCGGGCCCCACGAGCATTCG
TGTGCACTTCCAGGCCGGCCGCTTCCACCTGGACGGCAGCCGCGAGACCTTCGACTGCCTCTTCGAGCTGCTGGAGCACT
ACGTGGCGGCGCCGCGCCGCATGTTGGGGGCCCCACTGCGCCAGCGCCGCGTGCGGCCGCTGCAGGAGCTGTGTCGCCAG
CGCATCGTGGCCGCCGTGGGTCGCGAGAACCTGGCACGCATCCCTCTTAACCCGGTACTCCGTGACTACCTGAGTTCCTT
CCCCTTCCAGATCTGACCGGCTGCCGCCGTGCCCGCAGCATTAAGTGGGAGCGCCTTATTATTTCTTATTATTAATTATT
ATTATTTTTcTGGAACCACGTGGGAGCCCTCCCCGCCTAGGTCGGAGGGAGTGGGTGTGGAGGGTGAGATGCCTCCCACT
TCTGGCTGGAGACCTTATCCCGCCTCTCGGGGGGCCTCCCCTCCTGGTGCTCCCTCCCGGTCCCCCTGGTTGTAGCAGCT
TGTGTCTGGGGCCAGGACCTGAACTCCACGCCTACCTCTCCATGTTTACATGTTCCCAGTATCTTTGCACAAACCAGGGG
TGGGGGAGGGTCTCTGGCTTCATTTTTCTGCTGTGCAGAATATTCTATTTTATATTTTTACATCCAGTTTAGATAATAAA
CTTTATTATGAAAGTTTTTTTTTTAAAGAAAAAAAAAAAAAAAAAAAA
```

FIGURE 30

Rat 25r DNA (coding 130-[illegible]8)

GGCACGGCTCCCGGCCCCGGAGCATGCGCGACAGCAGCCCCGGAACCCCCAGCCGCGGCGCCCCGCGTCCCGCCGCCAGC
GCAGCCCCGGACGCTATGGCCCACCCCTCCAGCTGGCCCCTCGAGTAGGATGGTAGCACGTAACCAGGTGGCAGCCGACA
ATGCGATCTCCCCGGCATCAGAGCCCCGACGGCGGCCAGAGCCATCCTCGTCCTCGTCTTCGTCCTCGCCGGCGGCCCCG
GCGCGTCCCCGGCCCTGCCCGGTGGTCCCGGCCCCGGCTCCGGGCGACACTCACTTCCGCACCTTCCGCTCCCACTCTGA
TTACCGGCGCATCACGCGGACCAGCGCTCTCCTGGACGCCTGCGGCTTCTACTGGGGACCCCTGAGCGTGCATGGGGCGC
ACGAACGGCTGCGTGCCGAGCCCGTGGGCACCTTCTTGGTGCGCGACAGTCGCCAGCGGAACTGCTTCTTCGCGCTCAGC
GTGAAGATGGCTTCGGGCCCCACGAGCATTCGTGTGCACTTCCAGGCCGGCCGCTTCCACCTGGACGGCAGCCGCGAGAC
CTTCGACTGCCTCTTCGAGCTGCTGGAGCACTACGTGGCGGCGCCGCGCCGCATGTTGGGGGCCCCACTGCGCCAGCGCC
GCGTGCGGCCGCTGCAGGAGCTGTGTCGCCAGCGCATCGTGGCCGCCGTGGGTCGCGAGAACCTGGCACGCATCCCTCTT
AACCCGGTACTCCGTGACTACCTGAGTTCCTTCCCCTTCCAGATCTGACCGGCTGCCGCCGTGCCCGCAGCATTAAGTGG
GAGCGCCTTATTATTTCTTATTATTAATTATTATTATTTTTCTGGAACCACGTGGGAGCCCTCCCCGCCTAGGTCGGAGG
GAGTGGGTGTGGAGGGTGAGATGCCTCCCACTTCTGGCTGGAGACCTTATCCCGCCTCTCGGGGGGCCTCCCCTCCTGGT
GCTCCCTCCCGGTCCCCCTGGTTGTAGCAGCTTGTGTCTGGGGCCAGGACCTGAACTCCACGCCTACCTCTCCATGTTTA
CATGTTCCCAGTATCTTTGCACAAACCAGGGGTGGGGGAGGGTCTCTGGCTTCATTTTTCTGCTGTGCAGAATATTCTAT
TTTATATTTTTACATCCAGTTTAGATAATAAACTTTATTATGAAAGTTTTTTTTTAAAAAAAAAAAAAAAAA

FIGURE 31

Rat 5p protein

MPSQMEHAMETMMLTFHRFAGEKNYLTKEDLRVLMEREFPGFLENQKDPLAVDKIMKDLDQCRDGKVGFQSFLSLVAGLI
IACNDYFVVHMKQKK

Rat 5p DNA (coding: 52-339)

CTTCCAAAGACTGCAGCGCCTCAGGGCCCAGGTTTCAACAGATTCTTCAAAATGCCATCCCAAATGGAGCATGCCATGGA
AACCATGATGCTTACATTTCACAGGTTTGCAGGGGAAAAAAACTACTTGACAAAGGAGGACCTGAGAGTGCTCATGGAAA
GGGAGTTCCCTGGGTTTTTGGAAAATCAAAAGGACCCTCTGGCTGTGGACAAAATAATGAAAGACCTGGACCAGTGCCGA
GATGGAAAAGTGGGCTTCCAGAGCTTTCTATCACTAGTGGCGGGGCTCATCATTGCATGCAATGACTATTTTGTAGTACA
CATGAAGCAGAAGAAGTAGGCCAACTGGAGCCCTGGTACCCACACCTTGATGCGTCCTCTCCCATGGGGTCAACTGAGGA
ATCTGCCCCACTGCTTCCTGTGAGCAGATCAGGACCCTTAGGAAATGTGCAAATAACATCCAACTCCAATTCGACAAGCA
GAGAAAGAAAAGTTAATCCAATGACAGAGGAGCTTTCGAGTTTTATATTGTTTGCATCCGGTTGCCCTCAATAAAGAAAG
TCTTTTTTTTTAAGTTCCGAAAAAAAAAAAAAAAAAAAAA

FIGURE 32

Rat 7q protein

MAYAYLFKYIIIGDTGVGKSCLLLQFTDKRFQPVHDLTIGVEFGARMITIDGKQIKLQIWDTAGQESFRSITRSYYRGAA
GALLVYDITRRDTFNHLTTWLEDARQHSNSNMVIMLIGNKSDLESRREVKKEEGEAFAREHGLIFMETSAKTASNVEEAF
INTAKEIYEKIQEGVFDINNEANGIKIGPQHAATNASHGGNQGGQQAGGGCC

Rat 7q DNA (coding 1-639)

ATGGCGTACGCCTATCTCTTCAAGTACATCATCATCGGCGACACAGGTGTTGGTAAATCGTGCTTATTGCTACAGTTTAC
AGACAAGAGGTTTCAGCCGGTGCATGACCTCACAATTGGTGTAGAGTTTGGTGCTCGAATGATAACCATTGATGGGAAAC
AGATAAAACTCCAGATCTGGGATACAGCAGGGCAGGAGTCCTTTCGTTCTATCACAAGGTCATATTACAGAGGTGCAGCG
GGGGCTTTACTAGTGTATGATATTACAAGGAGAGACACGTTCAACCACTTGACAACCTGGTTAGAAGACGCCCGTCAGCA
TTCCAATTCCAACATGGTCATCATGCTTATTGGAAATAAAAGTGACTTAGAATCTAGGAGAGAAGTGAAAAAGGAAGAAG
GTGAAGCTTTTGCACGAGAGCATGGACTTATCTTCATGGAAACTTCTGCCAAGACTGCTTCTAATGTAGAGGAGGCATTT
ATTAACACAGCAAAAGAAATTTATGAAAAAATCCAAGAAGGGGTCTTTGACATTAATAATGAGGCAAACGGCATCAAAAT
TGGCCCTCAGCATGCTGCTACCAATGCATCTCACGGAGGCAACCAAGGAGGGCAGCAGGCAGGGGGAGGCTGCTGCTGA

FIGURE 33

Rat 19r protein
MVLLKEYRVILPVSVDEYQVGQLYSVAEASKNETGGGEGVEVLVNEPYEKDDGEKGQYTHKIYHLQSKVPTFVRMLAPEG
ALNIHEKAWNAYPYCRTVITNEYMKEDFLIKIETWHKPDLGTQENVHKLEPEAWKHVEAIYIDIADRSQVLSKDYKAEED
PAKFKSIKTGRGPLGPNWKQELVNQKDCPYMCAYKLVTVKFKWWGLQNKVENFIHKQEKRLFTNFHRQLFCWLDKWVDLT
MDDIRRMEEETKRQLDEMRQKDPVKGMTADD

Rat 19r DNA (coding 1-816)
ATGGTGCTGCTCAAGGAATATCGGGTCATCCTGCCTGTGTCTGTAGATGAGTATCAAGTGGGGCAGCTGTACTCTGTGGC
TGAAGCCAGTAAAAATGAAACTGGTGGTGGGGAAGGTGTGGAGGTCCTGGTGAACGAGCCCTACGAGAAGGATGATGGCG
AGAAAGGCCAGTACACACACAAGATCTACCACTTACAGAGCAAAGTTCCCACGTTTGTTCGAATGCTGGCCCCAGAAGGC
GCCCTGAATATACATGAGAAAGCCTGGAATGCCTACCCTTACTGCAGAACCGTTATTACAAATGAGTACATGAAGGAAGA
CTTTCTCATTAAAATTGAAACCTGGCACAAGCCAGACCTTGGCACCCAGGAGAATGTGCATAAACTGGAGCCTGAGGCAT
GGAAACATGTGGAAGCTATATATATAGACATCGCTGATCGAAGCCAAGTACTTAGCAAGGATTACAAGGCAGAGGAAGAC
CCAGCAAAATTTAAATCTATCAAAACAGGACGAGGACCATTGGGCCCGAATTGGAAGCAAGAACTTGTCAATCAGAAGGA
CTGCCCATATATGTGTGCATACAAACTGGTTACTGTCAAGTTCAAGTGGTGGGGCTTGCAGAACAAAGTGGAAAACTTTA
TACATAAGCAAGAGAAGCGTCTGTTTACAAACTTTCACAGGCAGCTGTTCTGTTGGCTTGATAAATGGGTTGATCTGACT
ATGGATGACATTCGGAGGATGGAAGAAGAGACGAAGAGACAGCTGGATGAGATGAGACAAAAGGACCCCGTGAAAGGAAT
GACAGCAGATGACTAG

FIGURE 34

Monkey KChIP4c (j1kxa053c02) DNA sequence (CD: 122-811)

CGCTCTCCTCCTCCCCTTTCTCTAGCAGTAGCCTTCTTAATGTAGTTTAATGGCTTTACAAAGAAAGCCAGGCAGAGGAG
CACTTCTCAGTGGCTGTGGTCGGACCATGACCTAGCTGACCATGAACTTGGAAGGGCTTGAAATGATAGCAGTTCTGATC
GTCATTGTGCTTTTTGTTAAATTATTGGAACAGTTTGGGCTGATTGAAGCAGGTTTAGAAGACAGCGTGGAAGATGAACT
GGAGATGGCCACTGTCAGGCATCGGCCTGAGGCCCTTGAGCTTCTGGAAGCCCAGAGCAAATTTACCAAGAAAGAGCTTC
AGATCCTTTACAGAGGATTTAAGAACGAATGCCCCAGTGGTGTTGTTAATGAAGAAACCTTCAAAGAGATTTACTCGCAG
TTCTTTCCACAGGGAGACTCTACAACATATGCACATTTTCTGTTCAATGCGTTTGATACGGACCACAATGGAGCTGTGAG
TTTCGAGGATTTCATCAAAGGTCTTTCCATTTTGCTCCGGGGGACAGTACAAGAAAAACTCAATTGGGCATTTAATCTGT
ATGATATAAATAAAGATGGCTACATCACTAAAGAGGAAATGCTTGATATAATGAAAGCAATATACGACATGATGGGTAAA
TGTACATATCCTGTCCTCAAAGAAGATGCACCCAGACAACACGTCGAAACATTTTTTCAGAAAATGGACAAAAATAAAGA
TGGGGTTGTTACCATAGATGAGTTCATTGAAAGCTGCCAAAAAGATGAAAACATAATGCGCTCCATGCAGCTCTTTGAAA
ATGTGATTTAACTTGTCAACTAGATCCTGAATCCAACAGACAAATGTGAACTATTCTACCACCCTTAAAGTCGGAGCTAC
CACTTTTAGCATAGATTGCTCAGCTTGACACTGAAGCATATTATGCAAACAAGCTTTGTTTAATATAAAGCAATCCCCA
AAAGATTTGAGTTTCTCAGTTATAAATTTGCATCCTTTCCATAATGCCACTGAGTTCATGGGATGTTCTAACTCATTTCA
TACTCTGTGAATATTCAAAAGTAATAGAATCTGGCATATAGTTTTATTGATTCCTTAGCCATGGGATTATTGAGGCTTTC
ACATATCAGTGATTTTAAAATACCAGTGTTTTTTGCTACTCATTTGTATGTATTCAGTCCTAGGATTTTGAATGGTTTTC
TAATATACTGACATCTGCATTTAATTTCCAGAAATTAAATTAATTTTCATGTCTGAATGCTGTAATTCCATTTATATACT
TTAAGTAAACAAATAAGATTACTACAATTAAACACATAGTTCCAGTTTCTATGGCCTTCACTTCCCACCTTCTATTAGAA
ATTAATTTTATCTGGTATTTTTAAACATTTAAAAATTTATCATCAGATATCAGCATATGCCTAATTATGCCTAATGAAAC
TTAATAAGCATTTAATTTTCCATCATACATTATAGTCAAGGCCTATATACTATATATAATTTTGGATTTGTTTAATCTTA
CAGGCTGTTTTCCATTGTATCATCAAGTGGAAGTTCAAGACGGCATCAAACAAAACAAGGATGTTTACAGACATATGCAA
AGGGTCAGGATATCTATCCTCCAGTATATGTTAATGCTTAATAACAGCTAATCCTAACAGCATTAAAGCCCAAATCTGTC
CTCTTTCCCCTGACTTCCTTACAGCATGTTTATATTACAACGCCATTCAGGGACAAAGAAACCTTGACTACCCCACTGTCT
ACTAGGAACAAACAAACAGCAAGCAAAATTCACTTTGAAAGCACCAGTGGTTCCATTACATTGACAACTACTACCAAGAT
TCAGTAGAAAATAAGTGCTCAACAACTAATCCAGATTACAATATGATTTAGTGCATCATAAAATTCCAACAATTCAGATT
ATTTTTAATCACCTCAGCCACAACTGTAAAGTTGCCACATTACTAAAGACACACACATCGTCCCTGTTTTGTAGAAATAT
CACAAAGACCAAGAGGCTACAGAAGGAGGAAATTTGCAACTGTCTTTGCAACAATAAATCAGGTATCTATTCTGGTGTAG
AGATAGGATGTTGAAAGCTGCCCTGCTATCACCAGTGTAGAAATTAAGAGTAGTACAATACATGTACACTGAAATTTGCC
ATCGCGTGTTTGTGTAAACTCAATGTGCACATTTTGTATTTCAAAAAGAAAAAATAAAAGCAAAATAAAATGTTTATAAC
TCTAAAAAAAAAAAAAAAAAAAA

Monkey KChIP4c protein sequence

MNLEGLEMIAVLIVIVLFVKLLEQFGLIEAGLEDSVEDELEMATVRHRPEALELLEAQSKFTKKELQILYRGFKNECPSG
VVNEETPKEIYSQFFPQGDSTTYAHFLFNAFDTDHNGAVSFEDFIKGLSILLRGTVQEKLNWAFNLYDINKDGYITKEEM
LDIMKAIYDMMGRCTYPVLKEDAPRQHVETFFQKMDKNKDGVVTIDEFIESCQKDENIMRSMQLFENVI.

FIGURE 35

Monkey KChIP4d (j1kx015b10) DNA sequence (CD:64-816)

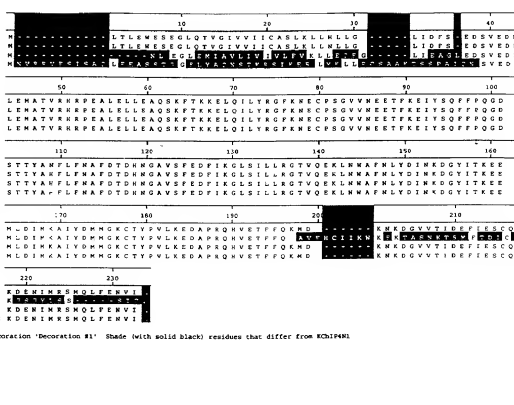
GTCGACAGACGCCCCTGGCCGGTGGACTCCTGAGTCTTACTCCTGCACCCTGCGTCCCCAGACATGAATGTGAGGAGAGT
GGAAAGCATTTCGGCTCAGCTGGAGGAGGCCAGCTCCACAGGCGGTTTCCTGTATGCTCAGAACAGCACCAAGCGCAGCA
TTAAAGAGCGGCTCATGAAGCTCTTGCCCTGCTCAGCTGCCAAAACATCGTCTCCTGCTATTCAAAACAGCGTGGAAGAT
GAACTGGAGATGGCCACTGTCAGGCATCGGCCTGAGGCCCTTGAGCTTCTGGAAGCCCAGAGCAAATTTACCAAGAAAGA
GCTTCAGATCCTTTACAGAGGATTTAAGAACGAATGCCCCAGTGGTGTTGTTAATGAAGAAACCTTCAAAGAGATTTACT
CGCAGTTCTTTCCACAGGGAGACTCTACAACATATGCACATTTTCTGTTCAATGCGTTTGATACGGACCACAATGGAGCT
GTGAGTTTCGAGGATTTCATCAAAGGTCTTTCCATTTTGCTCCGGGGGACAGTACAACGAAAAACTCAATTGGGCATTTAA
TCTGTATGATATAAATAAAGATGGCTACATCACTAAAGAGGAAATGCTTGATATAATGAAGCAATATACGACATGATGG
GTAAATGTACATATCCTGTCCTCAAAGAAGATGCACCCAGACAACACGTCGAAACATTTTTTCAGAAAATGGACAAAAAT
AAAGATGGGGTTGTTACCATAGATGAGTTCATTGAAAGCTGCCAAAAAGATGAAAACATAATGCGCTCCATGCAGCTCTT
TGAAAATGTGATTTAACTTGTCAACTAGATCCTGAATCCAACAGACAAATGTGAACTATTCTACCACCCTTAAAGTCGGA
GCTACCACTTTTAGCATAGATTGCTCAGCTTGACACTGAAGCATATTATGCAAACAAGCTTTGTTTTAATATAAAGCAAT
CCCCAAAAGATTTGAGTTTCTCAGTTATAAAATTTGCATCCTTTCCATAATGCCACTGAGTTCATGGGATGTTCTGACTCA
TTTCATACTCTGTGAATATTCAAAAGTAATAGAATCTGGCATATAGTTTTATTGATTCCTTAGCCATGGGATTATTGAGG
CTTTCACATATCAGTGATTTTAAAATACCAGTGTTTTTTGCTACTCATTTGTATGTATTCAGTCCTAGGATTTTGAATGG
TTTTCTAATATACTGACATCTGCATTTAATTTCCAGAAATTAAATTAATTTTCATGTCTGAATGCTGTAATTCCATTTAT
ATACTTTAAGTAAACAAATAAGATTACTACAATTAAACACATAGTTCCAGTTTCTATGGCCTTCACTTCCCACCTTCTAT
TAGAAATTAATTTTATCTGGTATTTTTAAACATTTAAAAATTTATCATCAGATATCAGCATATGCCTAATTATGCCTAAT
GAAACTTAATAAGCATTTAATTTTCCATCATACATTATAGTCAAGGCCTATATACTATATATAATTTTGGATTTGTTTAA
TCTTACAGGCTGTTTTCCATTGTATCATCAAGTGGAAGTTCAAGACGGCATCAAACAAAACAAGGATGTTTACAGACATA
TGCAAAGGGTCAGGATATCTATCCTCCAGTATATGTTAATGCTTAATAACAAGTAATCCTAACAGCATTAAAGGCCAAAT
CTGTCCTCTTTCCCCTGACTTCCTTACAGCATGTTTATATTACAAGCCATTCAGGGACAAAGAACCTTGACTACCCCAC
TGTCTACTAGGAACAAACAACAGCAAGCAAATTCACTTTGAAAGCACCAGTGGTTCCATTACATTGACAACTACTACC
AAGATTCAGTAGAAAATAAGTGCTCAACAACTAATCCAGATTACAATATGATTTAGTGCATCATAAAATTCCAACAATTC
AGATTATTTTTAATCACCTCAGCCACAACTGTAAAGTTGCCACATTACTAAAGACACACACATCGTCCCTGTTTTGTAGA
AATATCACAAAGACCAAGAGGCTACAGAAGGAGGAAATTTGCAACTGTCTTTGCAACAATAAATCAGGTATCTATTCTGG
TGTAGAGATAGGATGTTGAAAGCTGCCCTGCTATCACCAGTGTAGAAATTAAGAGTAGTACAATACATGTACACTGAAAT
TTGCCATCGCGTGTTTGTGTAAACTCAATGTGCACATTTTGTATTTCAAAAAGAAAAAATAAAAGCAAAATAAAATGTTA
AAAAAAAAAAAAAAAAAAA

Monkey KChIP4d protein sequence

MNVRRVESISAQLEEAASSTGGFLYAQNSTKRSIKERLMKLLPCSAAKTSSPAIQNSVEDELEMATVRHRPEALELLEAQS
KFTKKELQILYRGFKNECPSGVVNEETFKEIYSQFFPQGDSTTYAHFLFNAFDTDHNGAVSFEDFIKGLSILLRGTVQEK
LNWAFNLYDINKDGYITKEEMLDIMKAIYDMMGKCTYPVLKEDAPRQHVETFFQKMDKNKDGVVTIDEFIESCQKDENIM
RSMQLFENVI.

FIGURE 36

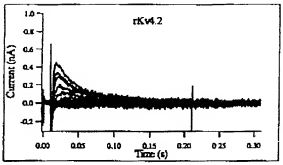
Alignment of monkey KChIP4

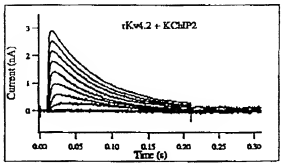


Decoration 'Decoration #1' Shade (with solid black) residues that differ from KChIP4N1

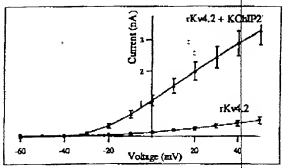
FIGURE 37

KChIP2 Expression Alters Kv4.2 Current





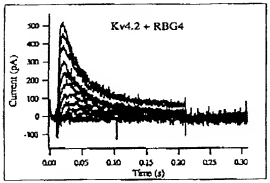
Voltage-Dependence

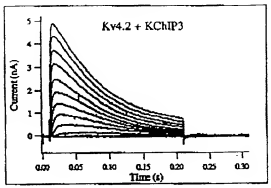


Current Parameter	CHO	
	rKv4.2	rKv4.2 +KChIP2
Peak Current (nA/cell, at 50 mV)	**0.51** ± 0.098	**3.3** ± 0.45
Peak Current Density (pA/pF, at 50 mV)	**18.6** ± 2.8	**196.6** ± 26.6
Inactivation time constant (ms, at 50 mV)	**28.47** ± 3.5	**95.14** ± 8.3
Recovery from Inactivation time constant (ms, at -80 mV)	**257.9**	**49.5**
Activation $V_{1/2}$ (mV)	**20.5**	**-2.2**
Steady-state Inactivation $V_{1/2}$ (mV)	**-47.1**	**-45.7**

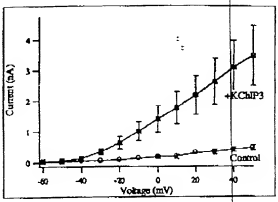
FIGURE 38

KChIP3 Expression Alters Kv4.2 Current





Voltage Dependence



Current Parameter	CHO	
	rKv4.2 +RBG4	rKv4.2 +KChIP3
Peak Current (nA/cell, at 50 mV)	0.46 ± 0.084	3.5 ± 0.99
Peak Current Density (pA/pF, at 50 mV)	29.7 ± 11.2	161.7 ± 21.8
Inactivation time constant (ms, at 50 mV)	29.5 ± 9.5	67.2 ± 14.1
Recovery from Inactivation time constant (ms, at -80 mV)	435.9	130.8
Activation $V_{1/2}$ (mV)	4.1	6.1

FIGURE 39

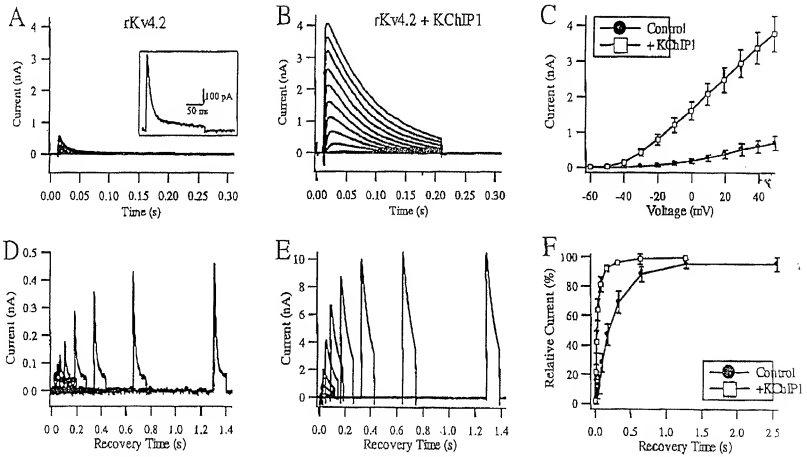


Figure 4D

```
h KChIP1 M G A - - - - - - - - - - - - V M G T F S S L Q T K Q R R P S K - - - - - - - - - - - - - - - - - - - - - - - - - - - -
h KChIP2 M R G Q G R K E S L S D S R D L D G S Y D Q L T G H P P G P T K K A L K - - - Q R F S K - - L L P C C G P Q - - - - A L
h KChIP3 M - - Q P A K E V - - - T K A S D G S L L G D L G H T P L S K K E G I K W Q R P R L S R Q A L M R C C L V K W I L S S T
h HIP    M G K Q N S K - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
r NCS1   M G K S N S K - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

                                                                                                               EF1
                                                                                                     X   Y   Z  -Y  -X    -Z
h KChIP1 - - - - - D K I E D E L E M T M V C H R P E G L E Q L E A Q T N F T K R E L Q V L Y R G F K N E C P S G V V N E D T F K
h KChIP2 P S V S E N S V D D E F E L S T V C H R P E G L E Q L Q E Q T K F T R K E L Q V L Y R G F K N E C P S G I V N E E N F K
h KChIP3 A P Q G S D S S D S E L E L S T V R H Q P E G L D Q L Q A Q T K F T K K E L Q S L Y R G F K N E C P T G L V D E D T F K
h HIP    - - - - - - - - - - - - - - - - - - L R P E M L Q D L R E N T E F S E L E L Q E W Y K G F L K D C P T G I L N V D E F K
r NCS1   - - - - - - - - - - - - - - - - - - L K P E V V E E L T R K T Y F T E K E V Q Q W Y K G F I K D C P S G Q L D A A G F Q

                                                                 EF2
                                                       X   Y   Z  -Y  -X    -Z                                                 X
h KChIP1 Q I Y A Q F F P H G D A S T Y A H Y L F N A F D T T Q T G S V K F E D F V T A L S I L L R G T V H E K L R W T F N L Y D
h KChIP2 Q I Y S Q F F P Q G D S S N Y A T F L F N A F D T N H D G S V S F E D F V A G L S V I L R G T V D D R L N W A F N L Y D
h KChIP3 L I Y A Q F F P Q G D A T T Y A H F L F N A F D A D G N G A I H F E D F V V G L S I L L R G T V H E K L K W A F N L Y D
h HIP    K I Y A N F F P Y G D A S K F A E H V F R T F D T N S D G T I D F R E F I I A L S V T S P G R L E Q K L M W A F S M Y D
r NCS1   K I Y K Q F F P F G D P T K F A T F V F N V F D E N K D G R I E F S E F I Q A L S V T S R G T L D E K L R W A F K L Y D

                 EF3                                                                                             EF4
           Y   Z  -Y  -X    -Z                                                                         X   Y   Z  -Y  -X    -Z
h KChIP1 I N K D G Y I N K E E M M D I V K A I Y D M M G K Y T Y P V L K E D T P R Q H V D V F F Q K M D K N K D G I V T L D E F
h KChIP2 L N K D G C I T K E E M L D I M K S I Y D M M G K Y T Y P A L R E E A P R E H V E S F F Q K M D R N K D G V V T I E E F
h KChIP3 I N K D G Y I T K E E M L A I M K S I Y D M M G R H T Y P I L R E D A P A E H V E R F F E K M D R N Q D G V V T I E E F
h HIP    L D G N G Y I S R E E M L E I V Q A I Y K M V S S V M K M P E D E S T P E K R T E K I F R Q M D T N N D G K L S L E E F
r NCS1   L D N D G Y I T R N E M L D I V D A I Y Q M V G N T V E L P E E E N T P E K R V D R I F A M M D K N A D G K L T L Q E F

h KChIP1 L E S C Q E D D N I M R S L Q - - - L F Q N V M .
h KChIP2 I E S C Q K D E N I M R S M Q - - - L F D N V I .
h KChIP3 L E A C Q K D E N I M S S M Q - - - L F E N V I .
h HIP    I R G A K S D P S I V R L L Q C D P S S R S Q F .
r NCS1   Q E G S K A D P S I V Q A L - - - S L Y D G L V .
```

FIGURE 4H

Customer Number: 000959

Attorney's
Docket
Number MNI-069CP

Declaration, Petition and Power of Attorney
for Continuation-in-Part Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

METHODS FOR TREATING CARDIOVASCULAR DISORDERS

the specification of which

(check one)

X is attached hereto.

__ was filed on _____ as

Application Serial No. _____

and was amended on _____.
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

This application in part discloses and claims subject matter disclosed in my earlier filed application(s), as follows:

X Serial No. 60/110,033 , filed November 25, 1998 ;
Serial No. 60/109,333 , filed November 20, 1998
Serial No. 60/110,277 , filed November 30, 1998 , as to which I claim priority benefit under Title 35, United States Code, §119(e).

X Serial No. 09/298,731 , filed April 23, 1999 ;
Serial No. 09/350,614 , filed July 9, 1999 ;
Serial No. 09/350,874 , filed July 9, 1999 , as to which I claim priority benefit under Title 35, United States Code, §120.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56, including all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of the continuation-in-part application.

AS TO PARENT APPLICATION:

As to the subject matter of this application which is common to said earlier application, I do not know and do not believe that the same was ever known or used in the United States of America before my or our invention thereof or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to said earlier application, or in public use or on sale in the United States of America more than one year prior to said earlier application; that the common subject matter has not been patented or made the subject of an inventor's certificate issued before the date of said earlier application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months prior to said earlier application; and

As to applications for patents or inventor's certificate or PCT international application(s) designating at least one country other than the United States of America, on the common subject matter, filed in or designating any country foreign to the United States of America, prior to said earlier application by me or my legal representatives or assigns,

Check one:

X no such applications have been filed.

_ such applications have been filed as follows

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID EARLIER U.S. APPLICATION

Country	Application Number	Date of Filing (month,day,year)	Priority Claimed Under 35 USC 119
			_ Yes No _
			_ Yes No _
			_ Yes No _
			_ Yes No _
			_ Yes No _

ALL FOREIGN APPLICATION(S), IF ANY, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID EARLIER U.S. APPLICATION

AS TO THIS APPLICATION:

As to the subject matter of this application which is not common to said earlier application, I do not know and do not believe that the same was ever known or used in the United States of America before my or our invention thereof or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to this application, or in public use or on sale in the United States of America more than one year prior to this application; that said non-common subject matter has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months prior to this application; and

As to applications for patents or inventor's certificate or PCT international application(s) designating at least one country other than the United States of America, on said non-common subject matter, filed in or designating any country foreign to the United States of America, prior to this application by me or my legal representatives or assigns,

Check one:

X no such applications have been filed.

_ such applications have been filed as follows

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

Country	Application Number	Date of Filing (month,day,year)	Priority Claimed Under 35 USC 119
			_ Yes No _
			_ Yes No _
			_ Yes No _
			_ Yes No _
			_ Yes No _

ALL FOREIGN APPLICATION(S), IF ANY, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

CLAIM FOR BENEFIT OF U.S. PROVISIONAL APPLICATION(S)

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

60/110,033	November 25, 1998
(Application Serial No.)	(Filing Date)
60/109,333	November 20, 1998
(Application Serial No.)	(Filing Date)
60/110,277	November 30, 1998
(Application Serial No.)	(Filing Date)

CLAIM FOR BENEFIT OF U.S. PATENT APPLICATION(S)

I hereby claim the benefit under 35 U.S.C. §120 of any United States patent application(s) listed below.

09/298,731	April 23, 1999
(Application Serial No.)	(Filing Date)
09/350,614	July 9, 1999
(Application Serial No.)	(Filing Date)
09/350,874	July 9, 1999
(Application Serial No.)	(Filing Date)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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James E. Cockfield	Reg. No. 19,162	Faustino A. Lichauco	Reg. No. 41,942
Thomas V. Smurzynski	Reg. No. 24,798	Jeanne M. DiGiorgio	Reg. No. 41,710
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Ann Lamport Hammitte	Reg. No. 34,858	Peter C. Lauro	Reg. No. 32,360
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Anthony A. Laurentano	Reg. No. 38,220	Timothy J. Douros	Reg. No. 41,716
Jane E. Remillard	Reg. No. 38,872	DeAnn F. Smith	Reg. No. 36,683
Jeremiah Lynch	Reg. No. 17,425	William D. DeVaul	Reg. No. 42,483
Kevin J. Canning	Reg. No. 35,470	David J. Rikkers	Reg. No. 43,882
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and to: Jean M. Silveri	Reg. No. 39,030	Cynthia Kanik	Reg. No. 37,320
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Send Correspondence to Amy E. Mandragouras at **Customer Number 000959** whose address is:

Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109

Direct Telephone Calls to: (name and telephone number)

Amy E. Mandragouras, (617) 227-7400

Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Citizenship U.S.
Post Office Address (if different)

Full name of second inventor, if any Wenqian An	
Inventor's signature	Date
Residence 1500 Worcester Rd. Apt. #212, Framingham, MA 01702	
Citizenship U.S.	
Post Office Address (if different)	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Kenneth Rhodes *et al.*

Serial No.: N/A

Filed: Herewith

For: *METHODS FOR TREATING CARDIOVASCULAR DISORDERS*

Attorney Docket No.: MNI-069CP

Assistant Commissioner for Patents
Box Sequence Listing
Washington, D.C. 20231

TRANSMITTAL LETTER FOR DISKETTE CONTAINING SEQUENCE LISTING

Dear Sir:

Enclosed is a diskette which contains a computer readable form of the Sequence Listing for the patent application filed herewith. The Sequence Listing complies with the requirements of 37 C.F.R. § 1.821. The material on this diskette is identical in substance to the sequence listing appearing on pages 1-92 of the Sequence Listing which is submitted herewith, as required by 37 C.F.R. § 1.821(f). The computer readable form of the Sequence Listing contained on the enclosed diskette is understood to comply with the requirements of § 1.824(d).

"Express Mail" mailing label number EL 266 739 835 US

Date of Deposit September 21, 1999

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Box Patent Application, Washington, D.C. 20231

Nelson Barros
Signature

NELSON BARROS
Please Print Name of Person Signing

LAHIVE & COCKFIELD, LLP
Attorneys at Law

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SEQUENCE LISTING

<110> Rhodes, Kenneth
An, Wenqian

<120> METHODS FOR TREATING CARDIOVASCULAR DISORDERS

<130> MNI-069CP

<140>
<141>

<150> USSN 60/110,277
<151> 1998-11-30

<150> USSN 60/110,033
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ttttctctcc tccaattcag agtagacaaa ccacggggat ttctttccag ggtaggggag 180

gggccgggcc cggggtccca actcgcactc aagtcttcgc tgcc atg ggg gcc gtc 236
Met Gly Ala Val
1

atg ggc acc ttc tca tct ctg caa acc aaa caa agg cga ccc tcg aaa 284
Met Gly Thr Phe Ser Ser Leu Gln Thr Lys Gln Arg Arg Pro Ser Lys
5 10 15 20

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gat aag att gaa gat gag ctg gag atg acc atg gtt tgc cat cgg ccc   332
Asp Lys Ile Glu Asp Glu Leu Glu Met Thr Met Val Cys His Arg Pro
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gag gga ctg gag cag ctc gag gcc cag acc aac ttc acc aag agg gag   380
Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg Glu
             40                  45                  50

ctg cag gtc ctt tat cga ggc ttc aaa aat gag tgc ccc agt ggt gtg   428
Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val
         55                  60                  65

gtc aac gaa gac aca ttc aag cag atc tat gct cag ttt ttc cct cat   476
Val Asn Glu Asp Thr Phe Lys Gln Ile Tyr Ala Gln Phe Phe Pro His
     70                  75                  80

gga gat gcc agc acg tat gcc cat tac ctc ttc aat gcc ttc gac acc   524
Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp Thr
 85                  90                  95                 100

act cag aca ggc tcc gtg aag ttc gag gac ttt gta acc gct ctg tcg   572
Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu Ser
                105                 110                 115

att tta ttg aga gga act gtc cac gag aaa cta agg tgg aca ttt aat   620
Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp Thr Phe Asn
            120                 125                 130

ttg tat gac atc aac aag gac gga tac ata aac aaa gag gag atg atg   668
Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met Met
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gac att gtc aaa gcc atc tat gac atg atg ggg aaa tac aca tat cct   716
Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro
    150                 155                 160

gtg ctc aaa gag gac act cca agg cag cat gtg gac gtc ttc ttc cag   764
Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val Phe Phe Gln
165                 170                 175                 180

aaa atg gac aaa aat aaa gat ggc atc gta act tta gat gaa ttt ctt   812
Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp Glu Phe Leu
                185                 190                 195

gaa tca tgt cag gag gac gac aac atc atg agg tct ctc cag ctg ttt   860
Glu Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu Gln Leu Phe
            200                 205                 210

caa aat gtc atg taactggtga cactcagcca ttcagctctc agagacattg       912
Gln Asn Val Met
        215

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tgggacagaa acacctttta cactttggaa gaattctctg ctgaagactt tcttatggaa 1032

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cccagcccac tgcctccaag tcaggcagac cttggtgaat ctggaagcaa gaggacctga 1272

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Cys His Arg Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe
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Pro Ser Gly Val Val Asn Glu Asp Thr Phe Lys Gln Ile Tyr Ala Gln
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Phe Phe Pro His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn
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Ala Phe Asp Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val
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Thr Ala Leu Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg
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Trp Thr Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys
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Glu Glu Met Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys

145                 150                 155                 160

Tyr Thr Tyr Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp
                165                 170                 175

Val Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu
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ggggaaataa aagcaaagat taccatgaat tgcaagatta cctagcaatt gcaaggtagg 180

aggagagagg tggagggcgg agtagacagg agggagggag aaagtgagag gaagctaggc 240

tggtggaaat aaccctgcac ttggaacagc ggcaaagaag cgcgattttc cagctttaa  299

atg cct gcc cgc gtt ctg ctt gcc tac ccg gga acg gag atg ttg acc    347
Met Pro Ala Arg Val Leu Leu Ala Tyr Pro Gly Thr Glu Met Leu Thr
 1               5                  10                  15

cag ggc gag tct gaa ggg ctc cag acc ttg ggg ata gta gtg gtc ctg    395
Gln Gly Glu Ser Glu Gly Leu Gln Thr Leu Gly Ile Val Val Val Leu
            20                  25                  30

tgt tcc tct ctg aaa cta ctg cac tac ctc ggg ctg att gac ttg tcg    443
Cys Ser Ser Leu Lys Leu Leu His Tyr Leu Gly Leu Ile Asp Leu Ser
        35                  40                  45

gat gac aag atc gag gat gat ctg gag atg acc atg gtt tgc cat cgg    491
Asp Asp Lys Ile Glu Asp Asp Leu Glu Met Thr Met Val Cys His Arg
    50                  55                  60

cct gag gga ctg gag cag ctt gag gca cag acg aac ttc acc aag aga    539
Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg
65                  70                  75                  80

gaa ctg caa gtc ctt tac cgg gga ttc aaa aac gag tgc ccc agt ggt    587
Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly
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gtg gtt aac gaa gag aca ttc aag cag atc tac gct cag ttt ttc cct    635
Val Val Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe Phe Pro
            100                 105                 110

cat gga gat gcc agc aca tac gca cat tac ctc ttc aat gcc ttc gac    683
His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp
        115                 120                 125

acc acc cag aca ggc tct gta aag ttc gag gac ttt gtg act gct ctg    731
Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu
    130                 135                 140

tcg att tta ctg aga gga acg gtc cat gaa aaa ctg agg tgg acg ttt    779
Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp Thr Phe
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atg gac ata gtg aaa gcc atc tat gac atg atg ggg aaa tac acc tat   875
Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr
            180                 185                 190

cct gtg ctc aaa gag gac act ccc agg cag cac gtg gac gtc ttc ttc   923
Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val Phe Phe
        195                 200                 205

cag aaa atg gat aaa aat aaa gat ggc att gta acg tta gac gaa ttt   971
Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp Glu Phe
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ctc gag tcc tgt cag gag gat gac aac atc atg agg tct cta cag ctg  1019
Leu Glu Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu Gln Leu
225                 230                 235                 240

ttc caa aat gtc atg taactgagga cactggccat cctgctctca gagacactga  1074
Phe Gln Asn Val Met
                245

caaacacctc aatgccctga tctgcccttg ttccagtttt acacatcaac tctcgggaca 1134

gaaatacctt ttacactttg gaagaattct ctgctgaaga ctttctacaa aacctggcac 1194

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Cys Ser Ser Leu Lys Leu Leu His Tyr Leu Gly Leu Ile Asp Leu Ser
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Asp Asp Lys Ile Glu Asp Asp Leu Glu Met Thr Met Val Cys His Arg
        50                  55                  60

Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg
 65                  70                  75                  80

Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly
                85                  90                  95

Val Val Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe Phe Pro
            100                 105                 110

His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp
        115                 120                 125

Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu
    130                 135                 140

Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp Thr Phe
145                 150                 155                 160

Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met
                165                 170                 175

Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr
            180                 185                 190

Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val Phe Phe
        195                 200                 205

Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp Glu Phe
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Gly Ala Val Met Gly Thr Phe Ser Ser Leu Gln Thr Lys Gln Arg Arg
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ccc tct aaa gac aag att gag gat gag cta gag atg acc atg gtt tgc 575
Pro Ser Lys Asp Lys Ile Glu Asp Glu Leu Glu Met Thr Met Val Cys
20 25 30

cac cgg cct gag gga ctg gag cag ctt gag gca cag acg aac ttc acc 623
His Arg Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr
35 40 45

aag aga gaa ctg caa gtc ttg tac cgg gga ttc aaa aac gag tgc cct 671
Lys Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro
50 55 60 65

agc ggt gtg gtc aat gaa gaa aca ttc aag cag atc tac gct cag ttt 719
Ser Gly Val Val Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe
70 75 80

ttc cct cac gga gat gcc agc aca tat gca cat tac ctc ttc aat gcc 767
Phe Pro His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala
85 90 95

ttc gac acc acc cag aca ggc tct gta aag ttc gag gac ttt gtg act 815
Phe Asp Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr
100 105 110

gct ctg tcg att tta ctg aga ggg aca gtc cat gaa aaa cta agg tgg 863
Ala Leu Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp
115 120 125

acg ttt aat ttg tat gac atc aat aaa gac ggc tac ata aac aaa gag 911
Thr Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu
130 135 140 145

gag atg atg gac ata gtc aaa gcc atc tat gac atg atg ggg aaa tac 959
Glu Met Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr
150 155 160

acc tat cct gtg ctc aaa gag gac act ccc agg cag cat gtg gat gtc 1007
Thr Tyr Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val
165 170 175

ttc ttc cag aaa atg gat aaa aat aaa gat ggc att gta acg tta gat 1055
Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp
180 185 190

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cag ctg ttc caa aat gtc atg taactgagga cactggccat tctgctctca       1154
Gln Leu Phe Gln Asn Val Met
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             20                  25                  30

Cys His Arg Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe
         35                  40                  45

Thr Lys Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys
     50                  55                  60

Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln
 65                  70                  75                  80

Phe Phe Pro His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn
                 85                  90                  95
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Trp Thr Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys
    130                 135                 140

Glu Glu Met Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys
145                 150                 155                 160

Tyr Thr Tyr Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp
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Val Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu
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Asp Glu Phe Leu Glu Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser
        195                 200                 205

Leu Gln Leu Phe Gln Asn Val Met
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Ser Ser Leu Gln Thr Lys Gln Arg Arg Pro Ser Lys Asp Ile Ala Trp
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Trp Tyr Tyr Gln Tyr Gln Arg Asp Lys Ile Glu Asp Asp Leu Glu Met
 25                  30                  35                  40

acc atg gtt tgc cat cgg cct gag gga ctg gag cag ctt gag gca cag   198
Thr Met Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln
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acg aac ttc acc aag aga gaa ctg caa gtc ctt tac cgg gga ttc aaa   246
Thr Asn Phe Thr Lys Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys
             60                  65                  70

aac gag tgc ccc agt ggt gtg gtt aac gaa gag aca ttc aag cag atc   294
Asn Glu Cys Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Gln Ile
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     90                  95                 100

ctc ttc aat gcc ttc gac acc acc cag aca ggc tct gta aag ttc gag   390
Leu Phe Asn Ala Phe Asp Thr Thr Gln Thr Gly Ser Val Lys Phe Glu
105                 110                 115                 120

gac ttt gtg act gct ctg tcg att tta ctg aga gga acg gtc cat gaa   438
Asp Phe Val Thr Ala Leu Ser Ile Leu Leu Arg Gly Thr Val His Glu
                125                 130                 135

aaa ctg agg tgg acg ttt aat ttg tac gac atc aat aaa gac ggc tac   486
Lys Leu Arg Trp Thr Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr
            140                 145                 150

ata aac aaa gag gag atg atg gac ata gtg aaa gcc atc tat gac atg   534
Ile Asn Lys Glu Glu Met Met Asp Ile Val Lys Ala Ile Tyr Asp Met
        155                 160                 165

atg ggg aaa tac acc tat cct gtg ctc aaa gag gac act ccc agg cag   582
Met Gly Lys Tyr Thr Tyr Pro Val Leu Lys Glu Asp Thr Pro Arg Gln
    170                 175                 180

cac gtg gac gtc ttc ttc cag aaa atg gat aaa aat aaa gat ggc att   630
His Val Asp Val Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Ile
185                 190                 195                 200

gta acg tta gac gaa ttt ctc gag tcc tgt cag gag gat gac aac atc   678
Val Thr Leu Asp Glu Phe Leu Glu Ser Cys Gln Glu Asp Asp Asn Ile
                205                 210                 215

atg agg tct cta cag ctg ttc caa aat gtc atg taactgagga cactggccat 731
Met Arg Ser Leu Gln Leu Phe Gln Asn Val Met
            220                 225

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35 40 45

Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg Glu Leu
50 55 60

Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val Val
65 70 75 80

Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe Phe Pro His Gly
85 90 95

Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp Thr Thr
100 105 110

Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu Ser Ile
115 120 125

Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp Thr Phe Asn Leu
130 135 140

Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met Met Asp
145 150 155 160

Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Val
165 170 175

Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val Phe Phe Gln Lys
180 185 190

Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp Glu Phe Leu Glu
195 200 205

Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu Gln Leu Phe Gln
210 215 220

Asn Val Met
225

<210> 9
<211> 1540
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (77)..(757)

<400> 9
atccacaccg atttcttttc aggggaggga agagacaggg cctggggtcc caagacgcac 60

acaagtcttc gctgcc atg ggg gcc gtc atg ggc act ttc tcc tcc ctg cag 112
Met Gly Ala Val Met Gly Thr Phe Ser Ser Leu Gln
1 5 10

acc aaa caa agg cga ccc tct aaa gac atc gcc tgg tgg tat tac cag 160
Thr Lys Gln Arg Arg Pro Ser Lys Asp Ile Ala Trp Trp Tyr Tyr Gln
15 20 25

tat cag aga gac aag att gag gat gag cta gag atg acc atg gtt tgc 208
Tyr Gln Arg Asp Lys Ile Glu Asp Glu Leu Glu Met Thr Met Val Cys
30 35 40

cac cgg cct gag gga ctg gag cag ctt gag gca cag acg aac ttc acc 256
His Arg Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr
45 50 55 60

aag aga gaa ctg caa gtc ttg tac cgg gga ttc aaa aac gag tgc cct 304
Lys Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro
65 70 75

agc ggt gtg gtc aat gaa gaa aca ttc aag cag atc tac gct cag ttt 352
Ser Gly Val Val Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe
80 85 90

ttc cct cac gga gat gcc agc aca tat gca cat tac ctc ttc aat gcc 400
Phe Pro His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala
95 100 105

ttc gac acc acc cag aca ggc tct gta aag ttc gag gac ttt gtg act 448
Phe Asp Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr
110 115 120

gct ctg tcg att tta ctg aga ggg aca gtc cat gaa aaa cta agg tgg 496
Ala Leu Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp
125 130 135 140

acg ttt aat ttg tat gac atc aat aaa gac ggc tac ata aac aaa gag 544
Thr Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu
145 150 155

gag atg atg gac ata gtc aaa gcc atc tat gac atg atg ggg aaa tac 592
Glu Met Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr
160 165 170

acc tat cct gtg ctc aaa gag gac act ccc agg cag cat gtg gat gtc 640
Thr Tyr Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val
175 180 185

ttc ttc cag aaa atg gat aaa aat aaa gat ggc att gta acg tta gat 688
Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp
190 195 200

```
gaa ttt ctt gaa tca tgt cag gag gat gac aac atc atg aga tct cta   736
Glu Phe Leu Glu Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu
205                 210                 215                 220

cag ctg ttc caa aat gtc atg taactgagga cactggccat tctgctctca      787
Gln Leu Phe Gln Asn Val Met
                225

gagacactga caaacacctt aatgccctga tctgcccttg ttccaatttt acacaccaac 847

tcttgggaca gaaatacctt ttacactttg gaagaattct ctgctgaaga ctttctacaa 907

aacctggcac cacgtggctc tgtctctgag ggacgagcgg agatccgact ttgttttgga 967

agcatgccca tctcttcatg ctgctgccct gtggaaggcc cctctgcttg agcttaatca 1027

atagtgcaca gttttatgct tacacatatc cccaactcac tgcctccaag tcaggcagac 1087

tctgatgaat ctgagccaaa tgtgcaccat cctccgatgg cctcccaagc caatgtgcct 1147

gcttctcttc ctctggtggg aagaaagagt gttctacgga acaattagag cttaccatga 1207

aaatattggg agaggcagca cctaacacat gtagaatagg actgaattat taagcatggt 1267

gatatcagat gatgcaaatt gcccatgtca ttttttttcaa aggtagggac aaatgattct 1327

cccacactag cacctgtggt catagagcaa gtctcttaac atgcccagaa ggggaaccac 1387

tgtccagtgg tctatccctc ctctccatcc cctgctcaaa cccagcactg catgtccctc 1447

caagaaggtc cagaatgcct gcgaaacgct gtacttttat accctgttct aatcaataaa 1507

cagaactatt tcgtacaaaa aaaaaaaaaa aaa                              1540


<210> 10
<211> 227
<212> PRT
<213> Mus musculus

<400> 10
Met Gly Ala Val Met Gly Thr Phe Ser Ser Leu Gln Thr Lys Gln Arg
  1               5                  10                  15

Arg Pro Ser Lys Asp Ile Ala Trp Trp Tyr Tyr Gln Tyr Gln Arg Asp
            20                  25                  30

Lys Ile Glu Asp Glu Leu Glu Met Thr Met Val Cys His Arg Pro Glu
        35                  40                  45

Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg Glu Leu
    50                  55                  60

Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val Val
65                  70                  75                  80

Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe Phe Pro His Gly
                85                  90                  95
```

```
Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp Thr Thr
            100                 105                 110

Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu Ser Ile
        115                 120                 125

Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp Thr Phe Asn Leu
    130                 135                 140

Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met Met Asp
145                 150                 155                 160

Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Val
                165                 170                 175

Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val Phe Phe Gln Lys
            180                 185                 190

Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp Glu Phe Leu Glu
        195                 200                 205

Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu Gln Leu Phe Gln
    210                 215                 220

Asn Val Met
225
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<210> 11
<211> 955
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (345)..(953)

<220>
<223> Xaa at position 92 of the corresponding amino acid sequence may be any amino acid

<400> 11

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tagttctctt ggctagcaga tgtttaggga ctggttaagc ctttggagaa attaccttag 120

gaaaacgggg aaataaaagc aaagattacc atgaattgca agattaccta gcaattgcaa 180

ggtaggagga gagaggtgga gggcggagta gacaggaggg agggagaaag tgagaggaag 240

ctaggctggt ggaaataacc ctgcacttgg aacagcggca aagaagcgcg attttccagc 300

tttaaatgcc tgcccgcgtt ctgcttgcct acccgggaac ggag atg ttg acc cag  356
                                                Met Leu Thr Gln
                                                  1

ggc gag tct gaa ggg ctc cag acc ttg ggg ata gta gtg gtc ctg tgt   404
Gly Glu Ser Glu Gly Leu Gln Thr Leu Gly Ile Val Val Val Leu Cys
  5                  10                  15                  20
```

```
tcc tct ctg aaa cta ctg cac tac ctc ggg ctg att gac ttg tcg gat   452
Ser Ser Leu Lys Leu Leu His Tyr Leu Gly Leu Ile Asp Leu Ser Asp
                 25                  30                  35

gac aag atc gag gat gat ctg gag atg acc atg gtt tgc cat cgg cct   500
Asp Lys Ile Glu Asp Asp Leu Glu Met Thr Met Val Cys His Arg Pro
             40                  45                  50

gag gga ctg gag cag ctt gag gca cag acg aac ttc acc aag aga gaa   548
Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg Glu
         55                  60                  65

ctg caa gtc ctt tac cgg gga ttc aaa aac gag tgc ccc agt ggt gtg   596
Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val
     70                  75                  80

gtt aac gaa gag aca ttc aag cng atc tac gct cag ttt ttc cct cat   644
Val Asn Glu Glu Thr Phe Lys Xaa Ile Tyr Ala Gln Phe Phe Pro His
 85                  90                  95                 100

gga gat gcc agc aca tac gca cat tac ctc ttc aat gcc ttc gac acc   692
Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp Thr
                105                 110                 115

acc cag aca ggc tct gta aag ttc gag gac ttt gtg act gct ctg tcg   740
Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu Ser
            120                 125                 130

att tta ctg aga gga acg gtc cat gaa aaa ctg aag tgg acg ttt aat   788
Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Lys Trp Thr Phe Asn
        135                 140                 145

ttg tac gac atc aat aaa gac ggc tac ata aac aaa gag gag atg atg   836
Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met Met
    150                 155                 160

gac ata gtg aaa gcc atc tat gac atg atg ggg aaa tac acc tat ctt   884
Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Leu
165                 170                 175                 180

gtg ctc aaa gag gac act tcc agg cag cac gtg gac gtc ttc ttc cag   932
Val Leu Lys Glu Asp Thr Ser Arg Gln His Val Asp Val Phe Phe Gln
                185                 190                 195

aaa atg gat aaa aat aaa gat gg                                   955
Lys Met Asp Lys Asn Lys Asp
            200
```

<210> 12
<211> 203
<212> PRT
<213> Rattus sp.

<400> 12

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Met Leu Thr Gln Gly Glu Ser Glu Gly Leu Gln Thr Leu Gly Ile Val
  1               5                  10                  15

Val Val Leu Cys Ser Ser Leu Lys Leu Leu His Tyr Leu Gly Leu Ile
             20                  25                  30
```

```
Asp Leu Ser Asp Asp Lys Ile Glu Asp Asp Leu Glu Met Thr Met Val
         35                  40                  45

Cys His Arg Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe
     50                  55                  60

Thr Lys Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys
 65                  70                  75                  80

Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Xaa Ile Tyr Ala Gln
                 85                  90                  95

Phe Phe Pro His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn
            100                 105                 110

Ala Phe Asp Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val
        115                 120                 125

Thr Ala Leu Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Lys
    130                 135                 140

Trp Thr Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys
145                 150                 155                 160

Glu Glu Met Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys
                165                 170                 175

Tyr Thr Tyr Leu Val Leu Lys Glu Asp Thr Ser Arg Gln His Val Asp
            180                 185                 190

Val Phe Phe Gln Lys Met Asp Lys Asn Lys Asp
        195                 200
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<210> 13
<211> 2009
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (207)..(1016)

<400> 13

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cgggcccatt cccagactca gcctcagccc ggacttcccc agccccgaca gcacagtagg 120

ccgccagggg gcgccgtgtg agcgccctat cccggccacc cggcgccccc tcccacggcc 180

cgggcgggag cggggcgccg ggggcc atg cgg ggc cag ggc cgc aag gag agt  233
                               Met Arg Gly Gln Gly Arg Lys Glu Ser
                                 1               5

ttg tcc gat tcc cga gac ctg gac ggc tcc tac gac cag ctc acg ggc   281
Leu Ser Asp Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly
 10                  15                  20                  25
```

```
cac cct cca ggg ccc act aaa aaa gcg ctg aag cag cga ttc ctc aag   329
His Pro Pro Gly Pro Thr Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys
                 30                  35                  40

ctg ctg ccg tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aca   377
Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Thr
             45                  50                  55

tta gcc gcc cca gcc tcc ctc cgc ccc cac aga ccc cgc ctg ctg gac   425
Leu Ala Ala Pro Ala Ser Leu Arg Pro His Arg Pro Arg Leu Leu Asp
         60                  65                  70

cca gac agc gtg gac gat gaa ttt gaa ttg tcc acc gtg tgt cac cgg   473
Pro Asp Ser Val Asp Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg
     75                  80                  85

cct gag ggt ctg gag cag ctg cag gag caa acc aaa ttc acg cgc aag   521
Pro Glu Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Lys
 90                  95                 100                 105

gag ttg cag gtc ctg tac cgg ggc ttc aag aac gaa tgt ccc agc gga   569
Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly
                110                 115                 120

att gtc aat gag gag aac ttc aag cag att tac tcc cag ttc ttt cct   617
Ile Val Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro
            125                 130                 135

caa gga gac tcc agc acc tat gcc act ttt ctc ttc aat gcc ttt gac   665
Gln Gly Asp Ser Ser Thr Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp
        140                 145                 150

acc aac cat gat ggc tcg gtc agt ttt gag gac ttt gtg gct ggt ttg   713
Thr Asn His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu
    155                 160                 165

tcc gtg att ctt cgg gga act gta gat gac agg ctt aat tgg gcc ttc   761
Ser Val Ile Leu Arg Gly Thr Val Asp Asp Arg Leu Asn Trp Ala Phe
170                 175                 180                 185

aac ctg tat gac ctt aac aag gac ggc tgc atc acc aag gag gaa atg   809
Asn Leu Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met
                190                 195                 200

ctt gac atc atg aag tcc atc tat gac atg atg ggc aag tac acg tac   857
Leu Asp Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr
            205                 210                 215

cct gca ctc cgg gag gag gcc cca agg gaa cac gtg gag agc ttc ttc   905
Pro Ala Leu Arg Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe
        220                 225                 230

cag aag atg gac aga aac aag gat ggt gtg gtg acc att gag gaa ttc   953
Gln Lys Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe
    235                 240                 245

att gag tct tgt caa aag gat gag aac atc atg agg tcc atg cag ctc  1001
Ile Glu Ser Cys Gln Lys Asp Glu Asn Ile Met Arg Ser Met Gln Leu
250                 255                 260                 265
```

```
ttt gac aat gtc atc tagcccccag gagaggggt cagtgtttcc tgggggacc   1056
Phe Asp Asn Val Ile
.               270

atgctctaac cctagtccag gcggacctca cccttctctt cccaggtcta tcctcatcct 1116

acgcctccct gggggctgga gggatccaag agcttgggga ttcagtagtc cagatctctg 1176

gagctgaagg ggccagagag tgggcagagt gcatctcggg gggtgttccc aactcccacc 1236

agctctcacc cccttcctgc ctgacaccca gtgttgagag tgcccctcct gtaggaattg 1296

agcggttccc cacctcctac cctactctag aaacacacta gagcgatgtc tcctgctatg 1356

gtgcttcccc catccctgac ctcataaaca tttcccctaa gactcccctc tcagagagaa 1416

tgctccattc ttggcactgg ctggcttctc agaccagcca ttgagagccc tgtgggaggg 1476

ggacaagaat gtatagggag aaatcttggg cctgagtcaa tggataggtc ctaggaggtg 1536

ggtggggttg agaatagaag ggcctggaca gattatgatt gctcaggcat accaggttat 1596

agctccaagt tccacaggtc tgctaccaca ggccatcaaa atataagttt ccaggctttg 1656

cagaagacct tgtctcctta gaaatgcccc agaaatttttc cacaccctcc tcggtatcca 1716

tggagagcct ggggccagat atctggctca tctctggcat tgcttcctct ccttccttcc 1776

tgcatgtgtt ggtggtggtt gtggtggggg aatgtggatg ggggatgtcc tggctgatgc 1836

ctgccaaaat ttcatcccac cctccttgct tatcgtccct gttttgaggg ctatgacttg 1896

agtttttgtt tcccatgttc tctatagact tgggaccttc ctgaacttgg ggcctatcac 1956

tccccacagt ggatgcctta gaagggagag ggaaggaggg aggcaggcat agc        2009
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<210> 14
<211> 270
<212> PRT
<213> Homo sapiens

<400> 14

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Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Asp Ser Arg Asp Leu
  1               5                  10                  15

Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly Pro Thr Lys
             20                  25                  30

Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
         35                  40                  45


Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro Ala Ser Leu
     50                  55                  60

Arg Pro His Arg Pro Arg Leu Leu Asp Pro Asp Ser Val Asp Asp Glu
 65                  70                  75                  80

Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu
                 85                  90                  95
```

```
Gln Glu Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg
            100                 105                 110

Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe
        115                 120                 125

Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr
    130                 135                 140

Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val
145                 150                 155                 160

Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr
                165                 170                 175

Val Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys
            180                 185                 190

Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile
        195                 200                 205

Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala
    210                 215                 220

Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys
225                 230                 235                 240

Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Lys Asp
                245                 250                 255

Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
            260                 265                 270


<210> 15
<211> 1247
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (2)..(772)

<400> 15
c cga gat ctg gac ggc tcc tat gac cag ctt acg ggc cac cct cca ggg 49
  Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly
  1               5                   10                  15

ccc agt aaa aaa gcc ctg aag cag cgt ttc ctc aag ctg ctg ccg tgc    97
Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys
            20                  25                  30

tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aca tta gct gcc cca    145
Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro
        35                  40                  45

gcc tcc ctc cgc ccc cac aga ccc cgc ccg ctg gac cca gac agc gta    193
Ala Ser Leu Arg Pro His Arg Pro Arg Pro Leu Asp Pro Asp Ser Val
    50                  55                  60
```

```
gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag ggc ctg   241
Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu
 65                  70                  75                  80

gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg cag gtc   289
Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val
                85                  90                  95

ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc aac gag   337
Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu
            100                 105                 110

gag aac ttc aag cag att tat tct cag ttc ttt ccc caa gga gac tcc   385
Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser
        115                 120                 125

agc aac tat gct act ttt ctc ttc aat gcc ttt gac acc aac cac gat   433
Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp
    130                 135                 140

ggc tct gtc agt ttt gag gac ttt gtg gct ggt ttg tcg gtg att ctt   481
Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu
145                 150                 155                 160

cgg ggg acc ata gat gat aga ctg agc tgg gct ttc aac tta tat gac   529
Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp
                165                 170                 175

ctc aac aag gac ggc tgt atc aca aag gag gaa atg ctt gac att atg   577
Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met
            180                 185                 190

aag tcc atc tat gac atg atg ggc aag tac aca tac cct gcc ctc cgg   625
Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg
        195                 200                 205

gag gag gcc cca aga gaa cac gtg gag agc ttc ttc cag aag atg gac   673
Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp
    210                 215                 220

agg aac aag gac ggc gtg gtg acc atc gag gaa ttc atc gag tct tgt   721
Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys
225                 230                 235                 240

caa cag gac gag aac atc atg agg tcc atg cag ctc ttt gat aat gtc   769
Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val
                245                 250                 255

atc tagctcccca gggagagggg ttagtgtgtc ctagggtgac caggctgtag        822
Ile

tcctagtcca gacgaaccta accctctctc tccaggcctg tcctcatctt acctgtaccc 882

tgggggctgt agggattcaa tatcctgggg cttcagtagt ccagatccct gagctaagtc 942

acaaaagtag gcaagagtag gcaagctaaa tctgggggct tcccaacccc cgacagctct 1002

caccccttct caactgatac ctagtgctga ggacacccct ggtgtaggga ccaagtggtt 1062

ctccaccttc tagtcccact ctagaaacca cattagacag aaggtctcct gctatggtgc 1122
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tttccccatc cctaatctct tagattttcc tcaagactcc cttctcagag aacacgctct 1182

gtccatgtcc ccagctgggg acatggacag agcgtgttct ctagttctag atcgcgagcg 1242

gccgc 1247

<210> 16
<211> 257
<212> PRT
<213> Rattus sp.

<400> 16

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Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly
  1               5                  10                  15

Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys
            20                  25                  30

Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro
        35                  40                  45

Ala Ser Leu Arg Pro His Arg Pro Arg Pro Leu Asp Pro Asp Ser Val
    50                  55                  60

Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu
65                  70                  75                  80

Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val
                85                  90                  95

Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu
            100                 105                 110

Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser
        115                 120                 125

Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp
    130                 135                 140

Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu
145                 150                 155                 160

Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp
                165                 170                 175

Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met
            180                 185                 190

Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg
        195                 200                 205

Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp
    210                 215                 220

Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys
225                 230                 235                 240

Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val
                245                 250                 255
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Ile

<210> 17
<211> 2343
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (181)..(990)

<400> 17
cgggactctg aggtgggccc taaaatccag cgctccccag agaaaagcct tgccagcccc 60

tactcccggc ccccagcccc agcaggtcgc tgcgccgcca gggggcactg tgtgagcgcc 120

ctatcctggc cacccggcgc cccctcccac ggcccaggcg ggagcggggc gccgggggcc 180

atg cgg ggc caa ggc cga aag gag agt ttg tcc gaa tcc cga gat ttg 228
Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Glu Ser Arg Asp Leu
1 5 10 15

gac ggc tcc tat gac cag ctt acg ggc cac cct cca ggg ccc agt aaa 276
Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly Pro Ser Lys
20 25 30

aaa gcc ctg aag cag cgt ttc ctc aag ctg ctg ccg tgc tgc ggg ccc 324
Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
35 40 45

caa gcc ctg ccc tca gtc agt gaa aca tta gct gcc cca gcc tcc ctc 372
Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro Ala Ser Leu
50 55 60

cgc ccc cac aga ccc cgc ccg ctg gac cca gac agc gtg gag gat gag 420
Arg Pro His Arg Pro Arg Pro Leu Asp Pro Asp Ser Val Glu Asp Glu
65 70 75 80

ttt gaa cta tcc acg gtg tgc cac cgg cct gag ggt ctg gaa caa ctc 468
Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu
85 90 95

cag gaa caa acc aag ttc aca cgc aga gag ttg cag gtc ctg tac aga 516
Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg
100 105 110

ggc ttc aag aac gaa tgt ccc agc gga att gtc aac gag gag aac ttc 564
Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe
115 120 125

aag caa att tat tct cag ttc ttt ccc caa gga gac tcc agc aac tac 612
Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr
130 135 140

gct act ttt ctc ttc aat gcc ttt gac acc aac cat gat ggc tct gtc 660
Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val
145 150 155 160

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agt ttt gag gac ttt gtg gct ggt ttg tca gtg att ctt cgg gga acc   708
Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr
                165                 170                 175

ata gat gat aga ctg aac tgg gct ttc aac tta tat gac ctc aac aag   756
Ile Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys
            180                 185                 190

gat ggc tgt atc acg aag gag gaa atg ctc gac atc atg aag tcc atc   804
Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile
        195                 200                 205

tat gac atg atg ggc aag tac acc tac cct gcc ctc cgg gag gag gcc   852
Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala
    210                 215                 220

ccg agg gaa cac gtg gag agc ttc ttc cag aag atg gac aga aac aag   900
Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys
225                 230                 235                 240

gac ggc gtg gtg acc att gag gaa ttc att gag tct tgt caa cag gac   948
Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Gln Asp
                245                 250                 255

gag aac atc atg agg tcc atg caa ctc ttt gat aat gtc atc           990
Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
            260                 265                 270

tagctcccca gggagagggg ttagtgtgtc ccagggtaac catgctgtag ccctagtcca 1050

ggcaaaccta accctcctct ccccgggtct gtcctcatcc tacctgtacc ctgggggctg 1110

tagggattca acatcctggc gcttcagtag tccagatccc tgagctaagt ggcgagagta 1170

ggcaagctaa gtctttggag ggtgggtggg ggcgcgcaga ttcccaaccc ccgacgactc 1230

tcacccctttt ctcgactgat acccagtgct gaggctaccc ctggtgtcgg gaacgaccaa 1290

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gaggggagaa taagaaagca gacaaaatct tggccctgag ccagtggtta ggtcctagga 1530

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tccagaaggc cttatgtcct tagcaatgtc ccagaaattc accatacact tctcagtgtc 1710

ttaggatcca gatgtccggt ccatccctga aacctctccc tcctccttgc tcctatggtg 1770

ggagtggtgg ccaggggacg atgagtgagc cggtgtcctg gatgatgcct gtcaaggtcc 1830

cacctaccct ccggctgtca agccgttctg gtgaccctgt ttgattctcc atgacccctg 1890

tctagatgta gaggtgtgga gtgagtctag tggcagcctt aggggaatgg gaagaacgag 1950

aggggcactc catctgaacc cagtgtgggg gcatccattc gaatctttgc ctggctcccc 2010
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acaatgccct aggatcctct agggtcccca cccccactct ttagtctacc cagagatgct 2070

ccagagctca cctagagggc agggaccata ggatccaggt ccaacctgtc atcagcatcc 2130

ggccatgctg ctgctgctta ttaataaacc tgcttgtcgt tcagcgcccc ttcccagtca 2190

gccagggtct gaggggaagg cccccacttt cccgcctcct gtcagacatt gttgactgct 2250

ttgcattttg ggctcttcta cctatatttt gtataataag aaagacacca gatccaataa 2310

aacacatggc tatgcacaaa aaaaaaaaaa aaa                              2343
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<210> 18
<211> 270
<212> PRT
<213> Mus musculus

<400> 18

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Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Glu Ser Arg Asp Leu
  1               5                  10                  15

Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly Pro Ser Lys
             20                  25                  30

Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
         35                  40                  45

Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro Ala Ser Leu
     50                  55                  60

Arg Pro His Arg Pro Arg Pro Leu Asp Pro Asp Ser Val Glu Asp Glu
 65                  70                  75                  80

Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu
                 85                  90                  95

Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg
            100                 105                 110

Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe
        115                 120                 125

Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr
    130                 135                 140

Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val
145                 150                 155                 160

Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr
                165                 170                 175

Ile Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys
            180                 185                 190

Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile
        195                 200                 205

Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala
    210                 215                 220
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Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys
225                 230                 235                 240

Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Gln Asp
                245                 250                 255

Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
            260                 265                 270


<210> 19
<211> 1955
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (207)..(962)

<400> 19
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cgggcccatt cccagactca gcctcagccc ggacttcccc agccccgaca gcacagtagg 120

ccgccagggg gcgccgtgtg agcgccctat cccggccacc cggcgccccc tcccacggcc 180

cgggcgggag cggggcgccg ggggcc atg cgg ggc cag ggc cgc aag gag agt  233
                               Met Arg Gly Gln Gly Arg Lys Glu Ser
                                 1               5

ttg tcc gat tcc cga gac ctg gac ggc tcc tac gac cag ctc acg ggc   281
Leu Ser Asp Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly
 10                  15                  20                  25

cac cct cca ggg ccc act aaa aaa gcg ctg aag cag cga ttc ctc aag   329
His Pro Pro Gly Pro Thr Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys
                30                  35                  40

ctg ctg ccg tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aac   377
Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Asn
            45                  50                  55

agc gtg gac gat gaa ttt gaa ttg tcc acc gtg tgt cac cgg cct gag   425
Ser Val Asp Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu
        60                  65                  70

ggt ctg gag cag ctg cag gag caa acc aaa ttc acg cgc aag gag ttg   473
Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Lys Glu Leu
    75                  80                  85

cag gtc ctg tac cgg ggc ttc aag aac gaa tgt ccc agc gga att gtc   521
Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val
 90                  95                  100                 105

aat gag gag aac ttc aag cag att tac tcc cag ttc ttt cct caa gga   569
Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly
                110                 115                 120
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gac tcc agc acc tat gcc act ttt ctc ttc aat gcc ttt gac acc aac   617
Asp Ser Ser Thr Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn
            125                 130                 135

cat gat ggc tcg gtc agt ttt gag gac ttt gtg gct ggt ttg tcc gtg   665
His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val
        140                 145                 150

att ctt cgg gga act gta gat gac agg ctt aat tgg gcc ttc aac ctg   713
Ile Leu Arg Gly Thr Val Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu
    155                 160                 165

tat gac ctt aac aag gac ggc tgc atc acc aag gag gaa atg ctt gac   761
Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp
170                 175                 180                 185

atc atg aag tcc atc tat gac atg atg ggc aag tac acg tac cct gca   809
Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala
                190                 195                 200

ctc cgg gag gag gcc cca agg gaa cac gtg gag agc ttc ttc cag aag   857
Leu Arg Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys
            205                 210                 215

atg gac aga aac aag gat ggt gtg gtg acc att gag gaa ttc att gag   905
Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu
        220                 225                 230

tct tgt caa aag gat gag aac atc atg agg tcc atg cag ctc ttt gac   953
Ser Cys Gln Lys Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp
    235                 240                 245

aat gtc atc tagcccccag gagagggggt cagtgtttcc tgggggacc           1002
Asn Val Ile
250

atgctctaac cctagtccag gcggacctca cccttctctt cccaggtcta tcctcatcct 1062

acgcctccct gggggctgga gggatccaag agcttgggga ttcagtagtc cagatctctg 1122

gagctgaagg ggccagagag tgggcagagt gcatctcggg gggtgttccc aactcccacc 1182

agctctcacc cccttcctgc ctgacaccca gtgttgagag tgcccctcct gtaggaattg 1242

agcggttccc cacctcctac cctactctag aaacacacta gagcgatgtc tcctgctatg 1302

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ggacaagaat gtatagggag aaatcttggg cctgagtcaa tggataggtc ctaggaggtg 1482

ggtggggttg agaatagaag ggcctggaca gattatgatt gctcaggcat accaggttat 1542

agctccaagt tccacaggtc tgctaccaca ggccatcaaa atataagttt ccaggctttg 1602

cagaagacct tgtctcctta gaaatgcccc agaaattttc cacaccctcc tcggtatcca 1662

tggagagcct ggggccagat atctggctca tctctggcat tgcttcctct ccttccttcc 1722
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tgcatgtgtt ggtggtggtt gtggtggggg aatgtggatg ggggatgtcc tggctgatgc 1782

ctgccaaaat ttcatcccac cctccttgct tatcgtccct gttttgaggg ctatgacttg 1842

agtttttgtt tcccatgttc tctatagact tgggaccttc ctgaacttgg ggcctatcac 1902

tccccacagt ggatgcctta gaagggagag ggaaggaggg aggcaggcat agc 1955

<210> 20
<211> 252
<212> PRT
<213> Homo sapiens

<400> 20
Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Asp Ser Arg Asp Leu
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Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly Pro Thr Lys
20 25 30

Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
35 40 45

Gln Ala Leu Pro Ser Val Ser Glu Asn Ser Val Asp Asp Glu Phe Glu
50 55 60

Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
65 70 75 80

Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg Gly Phe
85 90 95

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
100 105 110

Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr Ala Thr
115 120 125

Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
130 135 140

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Val Asp
145 150 155 160

Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
165 170 175

Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
180 185 190

Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
195 200 205

Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
210 215 220

Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Lys Asp Glu Asn
225 230 235 240

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Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
                245                 250


<210> 21
<211> 2300
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (214)..(969)

<400> 21
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cagcgctctc taaagaaaag ccttgccagc ccctactccc ggcccccaac cccagcaggt 120

cgctgcgccg ccaggggcgc ctgtgtgagc gccctattct ggccacccgg cgccccctcc 180

cacggcccag gcgggagcgg ggcgccgggg gcc atg cgg ggc caa ggc aga aag  234
                                    Met Arg Gly Gln Gly Arg Lys
                                      1               5

gag agt ttg tcc gaa tcc cga gat ctg gac ggc tcc tat gac cag ctt   282
Glu Ser Leu Ser Glu Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu
          10                  15                  20

acg ggc cac cct cca ggg ccc agt aaa aaa gcc ctg aag cag cgt ttc   330
Thr Gly His Pro Pro Gly Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe
     25                  30                  35

ctc aag ctg ctg ccg tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt   378
Leu Lys Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser
 40                  45                  50                  55

gaa aac agc gta gag gat gag ttt gaa tta tcc acg gtg tgt cac cga   426
Glu Asn Ser Val Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg
                 60                  65                  70

cct gag ggc ctg gaa caa ctc cag gaa cag acc aag ttc aca cgc aga   474
Pro Glu Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg
             75                  80                  85

gag ctg cag gtc ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg   522
Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly
         90                  95                  100

att gtc aac gag gag aac ttc aag cag att tat tct cag ttc ttt ccc   570
Ile Val Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro
    105                 110                 115

caa gga gac tcc agc aac tat gct act ttt ctc ttc aat gcc ttt gac   618
Gln Gly Asp Ser Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp
120                 125                 130                 135

acc aac cac gat ggc tct gtc agt ttt gag gac ttt gtg gct ggt ttg   666
Thr Asn His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu
                140                 145                 150
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tcg gtg att ctt cgg ggg acc ata gat gat aga ctg agc tgg gct ttc    714
Ser Val Ile Leu Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe
            155                 160                 165

aac tta tat gac ctc aac aag gac ggc tgt atc aca aag gag gaa atg    762
Asn Leu Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met
        170                 175                 180

ctt gac att atg aag tcc atc tat gac atg atg ggc aag tac aca tac    810
Leu Asp Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr
    185                 190                 195

cct gcc ctc cgg gag gag gcc cca aga gaa cac gtg gag agc ttc ttc    858
Pro Ala Leu Arg Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe
200                 205                 210                 215

cag aag atg gac agg aac aag gac ggc gtg gtg acc atc gag gaa ttc    906
Gln Lys Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe
                220                 225                 230

atc gag tct tgt caa cag gac gag aac atc atg agg tcc atg cag ctc    954
Ile Glu Ser Cys Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu
            235                 240                 245

ttt gat aat gtc atc tagctcccca gggagagggg ttagtgtgtc ctagggtgac   1009
Phe Asp Asn Val Ile
        250

caggctgtag tcctagtcca gacgaaccta accctctctc tccaggcctg tcctcatctt 1069

acctgtaccc tgggggctgt agggattcaa tatcctgggg cttcagtagt ccagatccct 1129

gagctaagtc acaaaagtag gcaagagtag gcaagctaaa tctgggggct tcccaacccc 1189

cgacagctct cacccccttct caactgatac ctagtgctga ggacacccct ggtgtaggga 1249

ccaagtggtt ctccaccttc tagtcccact ctagaaacca cattagacag aaggtctcct 1309

gctatggtgc tttccccatc cctaatctct tagattttcc tcaagactcc cttctcagag 1369

aacacgctct gtccatgtcc ccagctggct tctcagccta gcctttgagg gccctgtggg 1429

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aggggaatgg gaagaaccca gtgtgggggc acccattaga atctttgccc ggctcctcac 1969
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aatgccctag ggtcccctag ggtacccgct ccctctgttt agtctaccca gagatgctcc 2029

tgagctcacc tagagggtag ggacggtagg ctccaggtcc aacctctcca ggtcagcacc 2089

ctgccatgct gctgctcctc attaacaaac ctgcttgtct cctcctgcgc cccttctcag 2149

tcagccaggg tctgagggga agggcctccc gtttccccat ccgtcagaca tggttgactg 2209

ctttgcattt tgggctcttc tatctatttt gtaaaataag acatcagatc caataaaaca 2269

cacggctatg cacaaaaaaa aaaaaaaaaa a 2300

<210> 22
<211> 252
<212> PRT
<213> Rattus sp.

<400> 22
Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Glu Ser Arg Asp Leu
1 5 10 15

Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly Pro Ser Lys
20 25 30

Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
35 40 45

Gln Ala Leu Pro Ser Val Ser Glu Asn Ser Val Glu Asp Glu Phe Glu
50 55 60

Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
65 70 75 80

Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe
85 90 95

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
100 105 110

Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr Ala Thr
115 120 125

Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
130 135 140

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Ile Asp
145 150 155 160

Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
165 170 175

Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
180 185 190

Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
195 200 205

Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
210 215 220

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Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Gln Asp Glu Asn
225                 230                 235                 240

Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
                245                 250


<210> 23
<211> 1859
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (207)..(866)

<400> 23
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ccgccagggg gcgccgtgtg agcgccctat cccggccacc cggcgccccc tcccacggcc 180

cgggcgggag cggggcgccg ggggcc atg cgg ggc cag ggc cgc aag gag agt  233
                              Met Arg Gly Gln Gly Arg Lys Glu Ser
                                1               5

ttg tcc gat tcc cga gac ctg gac ggc tcc tac gac cag ctc acg gac   281
Leu Ser Asp Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Asp
 10                  15                  20                  25

agc gtg gac gat gaa ttt gaa ttg tcc acc gtg tgt cac cgg cct gag   329
Ser Val Asp Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu
                 30                  35                  40

ggt ctg gag cag ctg cag gag caa acc aaa ttc acg cgc aag gag ttg   377
Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Lys Glu Leu
             45                  50                  55

cag gtc ctg tac cgg ggc ttc aag aac gaa tgt ccc agc gga att gtc   425
Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val
         60                  65                  70

aat gag gag aac ttc aag cag att tac tcc cag ttc ttt cct caa gga   473
Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly
     75                  80                  85

gac tcc agc acc tat gcc act ttt ctc ttc aat gcc ttt gac acc aac   521
Asp Ser Ser Thr Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn
 90                  95                 100                 105

cat gat ggc tcg gtc agt ttt gag gac ttt gtg gct ggt ttg tcc gtg   569
His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val
                110                 115                 120

att ctt cgg gga act gta gat gac agg ctt aat tgg gcc ttc aac ctg   617
Ile Leu Arg Gly Thr Val Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu
            125                 130                 135
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tat gac ctt aac aag gac ggc tgc atc acc aag gag gaa atg ctt gac   665
Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp
        140                 145                 150

atc atg aag tcc atc tat gac atg atg ggc aag tac acg tac cct gca   713
Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala
    155                 160                 165

ctc cgg gag gag gcc cca agg gaa cac gtg gag agc ttc ttc cag aag   761
Leu Arg Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys
170                 175                 180                 185

atg gac aga aac aag gat ggt gtg gtg acc att gag gaa ttc att gag   809
Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu
                190                 195                 200

tct tgt caa aag gat gag aac atc atg agg tcc atg cag ctc ttt gac   857
Ser Cys Gln Lys Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp
            205                 210                 215

aat gtc atc tagcccccag gagagggggt cagtgtttcc tgggggacc           906
Asn Val Ile
        220

atgctctaac cctagtccag gcggacctca cccttctctt cccaggtcta tcctcatcct 966

acgcctccct gggggctgga gggatccaag agcttgggga ttcagtagtc cagatctctg 1026

gagctgaagg ggccagagag tgggcagagt gcatctcggg gggtgttccc aactcccacc 1086

agctctcacc cccttcctgc ctgacaccca gtgttgagag tgcccctcct gtaggaattg 1146

agcggttccc cacctcctac cctactctag aaacacacta gagcgatgtc tcctgctatg 1206

gtgcttcccc catccctgac ctcataaaca tttcccctaa gactcccctc tcagagagaa 1266

tgctccattc ttggcactgg ctggcttctc agaccagcca ttgagagccc tgtgggaggg 1326

ggacaagaat gtatagggag aaatcttggg cctgagtcaa tggataggtc ctaggaggtg 1386

ggtggggttg agaatagaag ggcctggaca gattatgatt gctcaggcat accaggttat 1446

agctccaagt tccacaggtc tgctaccaca ggccatcaaa atataagttt ccaggctttg 1506

cagaagacct tgtctcctta gaaatgcccc agaaattttc cacaccctcc tcggtatcca 1566

tggagagcct ggggccagat atctggctca tctctggcat tgcttcctct ccttccttcc 1626

tgcatgtgtt ggtggtggtt gtggtggggg aatgtggatg ggggatgtcc tggctgatgc 1686

ctgccaaaat ttcatcccac cctccttgct tatcgtccct gttttgaggg ctatgacttg 1746

agtttttgtt tcccatgttc tctatagact tgggaccttc ctgaacttgg ggcctatcac 1806

tccccacagt ggatgcctta gaagggagag ggaaggaggg aggcaggcat agc        1859
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<210> 24
<211> 220
<212> PRT
<213> Homo sapiens

<400> 24
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1 5 10 15

Asp Gly Ser Tyr Asp Gln Leu Thr Asp Ser Val Asp Asp Glu Phe Glu
20 25 30

Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
35 40 45

Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg Gly Phe
50 55 60

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
65 70 75 80

Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr Ala Thr
85 90 95

Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
100 105 110

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Val Asp
115 120 125

Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
130 135 140

Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
145 150 155 160

Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
165 170 175

Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
180 185 190

Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Lys Asp Glu Asn
195 200 205

Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
210 215 220

<210> 25
<211> 2191
<212> DNA
<213> Simian sp.

<220>
<221> CDS
<222> (133)..(792)

<400> 25

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cgtgtgagcg ccctatcccg gccacccggc gccccctccc acggaccggg cgggagcggg 120

gcgccgggggg cc atg cgg ggc cag ggc cgc aag gag agt ttg tcc gat tcc 171
              Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Asp Ser
                1               5                  10

cga gac ctg gac gga tcc tac gac cag ctc acg gac agc gtg gag gat   219
Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Asp Ser Val Glu Asp
     15                  20                  25

gaa ttt gaa ttg tcc acc gtg tgt cac cgg cct gag ggt ctg gag cag   267
Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln
 30                  35                  40                  45

ctg cag gag caa acc aaa ttc acg cgc aag gag ttg cag gtc ctg tac   315
Leu Gln Glu Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr
                 50                  55                  60

cgg ggc ttc aag aac gaa tgt ccg agc gga att gtc aat gag gag aac   363
Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn
             65                  70                  75

ttc aag caa att tac tcc cag ttc ttt cct caa gga gac tcc agc acc   411
Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr
         80                  85                  90

tat gcc act ttt ctc ttc aat gcc ttt gac acc aac cat gat ggc tcg   459
Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser
     95                  100                 105

gtc agt ttt gag gac ttt gtg gct ggt ttg tcc gtg att ctt cgg gga   507
Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly
110                 115                 120                 125

act gta gat gac agg ctt aat tgg gcc ttc aac ttg tat gac ctc aac   555
Thr Val Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn
                130                 135                 140

aag gac ggc tgc atc acc aag gag gaa atg ctt gac atc atg aag tcc   603
Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser
            145                 150                 155

atc tat gac atg atg ggc aag tac aca tac cct gca ctc cgg gag gag   651
Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu
        160                 165                 170

gcc cca agg gaa cat gtg gag aac ttc ttc cag aag atg gac aga aac   699
Ala Pro Arg Glu His Val Glu Asn Phe Phe Gln Lys Met Asp Arg Asn
    175                 180                 185

aag gat ggc gtg gtg acc att gag gaa ttc att gag tct tgt caa aag   747
Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Lys
190                 195                 200                 205

gat gag aac atc atg agg tcc atg cag ctc ttt gac aat gtc atc       792
Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
                210                 215                 220
```

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tagcccccag gagaggggggt cagtgtttcc tggggggacc atgctctaac cctagtccag 852
gtggacctca cccttctctt cccaggtcta tccttgtcct aggcctccct gggggctgga 912
gggatccaag agcttgggga ttcagtagtc cagatctctg gagctgaagg ggccagagag 972
tgggcagagt gcatcttggg gggtgttccc aactcccacc agctttcacc cgcttcctgc 1032
ctgacaccca gtgttgagag tgcccctcct gtaggaactg agtggttccc cacctcctac 1092
ccccactcta gaaacacact agacagatgt ctcctgctat ggtgcttccc ccatccctga 1152
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gctggcttct cagaccagcc tttgagagcc ctgtgggagg gggacaagaa tgtatagggg 1272
agaaatcttg ggcctgagtc aatggatagg tcctaggagg tggctggggt tgagaataga 1332
aaggcctgga cacaatgtga ttgctcaggc ataccaagtt atagctccaa gttccacagg 1392
tctgctacca caggccatca aaatataagt ttccaggctt tgcagaagac cttgtctcct 1452
tggaaatgcc ccagatattt tccataccct cctcgatatc catggagagc ctggggctag 1512
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tagagtctcc tcttgctcta ctcaatctac ccagagatgc cccttagcac actcagaggg 1932
cagggaccat aggacccagg ttccaacccc attgtcagca ccccagccat gctgccatcc 1992
cttagcacac ctgctcgtcc cattcagctt accctcccag tcagccagaa tctgagggga 2052
gggcccccag agagcccccct tccccatcag aagactgttg actgctttgc attttgggct 2112
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aaaaaaaaaa aaaaaaaaa                                              2191
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<210> 26
<211> 220
<212> PRT
<213> Simian sp.

<400> 26

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Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Asp Ser Arg Asp Leu
 1               5                  10                  15

Asp Gly Ser Tyr Asp Gln Leu Thr Asp Ser Val Glu Asp Glu Phe Glu
            20                  25                  30
```

Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
35 40 45

Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg Gly Phe
50 55 60

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
65 70 75 80

Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr Ala Thr
85 90 95

Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
100 105 110

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Val Asp
115 120 125

Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
130 135 140

Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
145 150 155 160

Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
165 170 175

Glu His Val Glu Asn Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
180 185 190

Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Lys Asp Glu Asn
195 200 205

Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
210 215 220

<210> 27
<211> 2057
<212> DNA
<213> Simian sp.

<220>
<221> CDS
<222> (208)..(963)

<400> 27
tgctgcccaa ggctcctgct cctgccccag gactctgagg tgggccctaa aacccagcgc 60

tctctaaaga aaagccttgc cagcccctac tcccggcccc caaccccagc aggtcgctgc 120

gccgccaggg ggcgctgtgt gagcgcccta ttctggccac ccggcgcccc ctcccacggc 180

ccaggcggga gcggggcgcc gggggcc atg cgg ggc caa ggc aga aag gag agt 234
Met Arg Gly Gln Gly Arg Lys Glu Ser
1 5

```
ttg tcc gaa tcc cga gat ctg gac ggc tcc tat gac cag ctt acg ggc   282
Leu Ser Glu Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly
 10                  15                  20                  25

cac cct cca ggg ccc agt aaa aaa gcc ctg aag cag cgt ttc ctc aag   330
His Pro Pro Gly Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys
             30                  35                  40

ctg ctg ccg tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aac   378
Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Asn
         45                  50                  55

agc gta gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag   426
Ser Val Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu
     60                  65                  70

ggc ctg gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg   474
Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu
 75                  80                  85

cag gtc ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc   522
Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val
 90                  95                 100                 105

aac gag gag aac ttc aag cag att tat tct cag ttc ttt ccc caa gga   570
Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly
                110                 115                 120

gac tcc agc aac tat gct act ttt ctc ttc aat gcc ttt gac acc aac   618
Asp Ser Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn
            125                 130                 135

cac gat ggc tct gtc agt ttt gag gac ttt gtg gct ggt ttg tcg gtg   666
His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val
        140                 145                 150

att ctt cgg ggg acc ata gat gat aga ctg agc tgg gct ttc aac tta   714
Ile Leu Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu
    155                 160                 165

tat gac ctc aac aag gac ggc tgt atc aca aag gag gaa atg ctt gac   762
Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp
170                 175                 180                 185

att atg aag tcc atc tat gac atg atg ggc aag tac aca tac cct gcc   810
Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala
                190                 195                 200

ctc cgg gag gag gcc cca aga gaa cac gtg gag agc ttc ttc cag aag   858
Leu Arg Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys
            205                 210                 215

atg gac agg aac aag gac ggc gtg gtg acc atc gag gaa ttc atc gag   906
Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu
        220                 225                 230

tct tgt caa cag gac gag aac atc atg agg tcc atg cag ctc tca ccc   954
Ser Cys Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Ser Pro
    235                 240                 245
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ctt ctc aac tgatacctag tgctgaggac acccctggtg tagggaccaa 1003
Leu Leu Asn
250

gtggttctcc accttctagt cccactctag aaaccacatt agacagaagg tctcctgcta 1063

tggtgctttc cccatcccta atctcttaga ttttcctcaa gactcccttc tcagagaaca 1123

cgctctgtcc atgtccccag ctggcttctc agcctagcct ttgagggccc tgtggggagg 1183

cggggacaag aaagcagaaa agtcttggcc ccgagccagt ggttaggtcc taggaattgg 1243

ctggagtgga ggccagaaag cctgggcaga tgatgagagc ccagctgggc tgtcactgca 1303

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ccttagcaat gtcccagaaa ttcaccgtac acttctcagt gtcttaggag ggcccgggat 1423

ccagatgtct ggttcatccc tgaatcctct ccctccttct tgctcgtatg gtgggagtgg 1483

tggccagggg aagatgagtg gtgtcccgga tgatgcctgt caaggtccca cctcccctcc 1543

ggctgttctc atgacagctg tttggttctc catgacccct atctagatgt agaggcatgg 1603

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gaatgggaag aacccagtgt gggggcaccc attagaatct ttgcccggct cctcacaatg 1723

ccctagggtc ccctagggta cccgctccct ctgtttagtc tacccagaga tgctcctgag 1783

ctcacctaga gggtagggac ggtaggctcc aggtccaacc tctccaggtc agcaccctgc 1843

catgctgctg ctcctcatta acaaacctgc ttgtctcctc ctgcgcccct tctcagtcag 1903

ccagggtctg aggggaaggg cctcccgttt ccccatccgt cagacatggt tgactgcttt 1963

gcattttggg ctcttctatc tattttgtaa aataagacat cagatccaat aaaacacacg 2023

gctatgcaca aaaaaaaaaa aaaaaaaaaa aaaa 2057

<210> 28
<211> 252
<212> PRT
<213> Simian sp.

<400> 28
Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Glu Ser Arg Asp Leu
1 5 10 15

Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly Pro Ser Lys
20 25 30

Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
35 40 45

Gln Ala Leu Pro Ser Val Ser Glu Asn Ser Val Glu Asp Glu Phe Glu
50 55 60

Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
65 70 75 80

```
Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe
                 85                  90                  95

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
            100                 105                 110

Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr Ala Thr
        115                 120                 125

Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
    130                 135                 140

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Ile Asp
145                 150                 155                 160

Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
                165                 170                 175

Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
            180                 185                 190

Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
        195                 200                 205

Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
    210                 215                 220


Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Gln Asp Glu Asn
225                 230                 235                 240

Ile Met Arg Ser Met Gln Leu Ser Pro Leu Leu Asn
                245                 250


<210> 29
<211> 1904
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (1)..(675)

<400> 29
atg aac cac tgc cct cgc agg tgc cgg agc ccg ttg ggg cag gca gct   48
Met Asn His Cys Pro Arg Arg Cys Arg Ser Pro Leu Gly Gln Ala Ala
  1               5                  10                  15

cga tct ctc tac cag ttg gta act ggg tcg ctg tcg cca gac agc gta   96
Arg Ser Leu Tyr Gln Leu Val Thr Gly Ser Leu Ser Pro Asp Ser Val
             20                  25                  30

gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag ggc ctg   144
Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu
         35                  40                  45

gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg cag gtc   192
Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val
     50                  55                  60
```

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ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc aac gag   240
Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu
 65                  70                  75                  80

gag aac ttc aag cag att tat tct cag ttc ttt ccc caa gga gac tcc   288
Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser
                85                  90                  95

agc aac tat gct act ttt ctc ttc aat gcc ttt gac acc aac cac gat   336
Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp
            100                 105                 110

ggc tct gtc agt ttt gag gac ttt gtg gct ggt ttg tcg gtg att ctt   384
Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu
        115                 120                 125

cgg ggg acc ata gat gat aga ctg agc tgg gct ttc aac tta tat gac   432
Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp
    130                 135                 140

ctc aac aag gac ggc tgt atc aca aag gag gaa atg ctt gac att atg   480
Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met
145                 150                 155                 160

aag tcc atc tat gac atg atg ggc aag tac aca tac cct gcc ctc cgg   528
Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg
                165                 170                 175

gag gag gcc cca aga gaa cac gtg gag agc ttc ttc cag aag atg gac   576
Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp
            180                 185                 190

agg aac aag gac ggc gtg gtg acc atc gag gaa ttc atc gag tct tgt   624
Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys
        195                 200                 205

caa cag gac gag aac atc atg agg tcc atg cag ctc ttt gat aat gtc   672
Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val
    210                 215                 220

atc tagctcccca gggagagggg ttagtgtgtc ctagggtgac caggctgtag        725
Ile
225

tcctagtcca gacgaaccta accctctctc tccaggcctg tcctcatctt acctgtaccc 785

tgggggctgt agggattcaa tatcctgggg cttcagtagt ccagatccct gagctaagtc 845

acaaaagtag gcaagagtag gcaagctaaa tctgggggct tcccaacccc cgacagctct 905

caccccttct caactgatac ctagtgctga ggacaccct ggtgtaggga ccaagtggtt 965

ctccaccttc tagtcccact ctagaaacca cattagacag aaggtctcct gctatggtgc 1025

tttccccatc cctaatctct tagattttcc tcaagactcc cttctcagag aacacgctct 1085

gtccatgtcc ccagctggct tctcagccta gcctttgagg gccctgtggg gaggcgggga 1145

caagaaagca gaaaagtctt ggccccgagc tagtggttag gtcctaggaa ttggctggag 1205
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tggaggccag aaagcctggg cagatgatga gagcccagct gggctgtcac tgcaggttcc 1265

agggcctaca gccctgggtc agcagagtat gagttcccag actttccaga aggtccttag 1325

caatgtccca gaaattcacc atacacttct cagtgtcccg gatgatgcct gtcaaggtcc 1385

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gatgctcctg agctcaccta gagggtaggg acggtaggct ccaggtccaa cctctccagg 1685

tcagcaccct gccatgctgc tgctcctcat taacaaacct gcttgtctcc tcctgcgccc 1745

cttctcagtc agccagggtc tgaggggaag ggcctcccgt ttccccatcc gtcagacatg 1805

gttgactgct ttgcattttg ggctcttcta tctattttgt aaaataagac atcagatcca 1865

ataaaacaca cggctatgca caaaaaaaaa aaaaaaaaa                          1904
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<210> 30
<211> 225
<212> PRT
<213> Rattus sp.

<400> 30

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Met Asn His Cys Pro Arg Arg Cys Arg Ser Pro Leu Gly Gln Ala Ala
  1               5                  10                  15

Arg Ser Leu Tyr Gln Leu Val Thr Gly Ser Leu Ser Pro Asp Ser Val
             20                  25                  30

Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu
         35                  40                  45

Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val
     50                  55                  60

Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu
 65                  70                  75                  80

Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser
                 85                  90                  95

Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp
            100                 105                 110

Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu
        115                 120                 125

Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp
    130                 135                 140

Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met
145                 150                 155                 160
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```
Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg
                165                 170                 175

Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp
            180                 185                 190

Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys
        195                 200                 205

Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val
    210                 215                 220

Ile
225
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<210> 31
<211> 2841
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(768)

<400> 31

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atg cag ccg gct aag gaa gtg aca aag gcg tcg gac ggc agc ctc ctg   48
Met Gln Pro Ala Lys Glu Val Thr Lys Ala Ser Asp Gly Ser Leu Leu
  1               5                  10                  15

ggg gac ctc ggg cac aca cca ctt agc aag aag gag ggt atc aaq tgg   96
Gly Asp Leu Gly His Thr Pro Leu Ser Lys Lys Glu Gly Ile Lys Trp
            20                  25                  30

cag agg ccg agg ctc agc cgc cag gct ttg atg aga tgc tgc ctg gtc   144
Gln Arg Pro Arg Leu Ser Arg Gln Ala Leu Met Arg Cys Cys Leu Val
        35                  40                  45

aag tgg atc ctg tcc agc aca gcc cca cag ggc tca gat agc agc gac   192
Lys Trp Ile Leu Ser Ser Thr Ala Pro Gln Gly Ser Asp Ser Ser Asp
    50                  55                  60

agt gag ctg gag ctg tcc acg gtg cgc cac cag cca gag ggg ctg gac   240
Ser Glu Leu Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp
65                  70                  75                  80

cag ctg cag gcc cag acc aag ttc acc aag aag gag ctg cag tct ctc   288
Gln Leu Gln Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu
                85                  90                  95

tac agg ggc ttt aag aat gag tgt ccc acg ggc ctg gtg gac gaa gac   336
Tyr Arg Gly Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp
            100                 105                 110

acc ttc aaa ctc att tac gcg cag ttc ttc cct cag gga gat gcc acc   384
Thr Phe Lys Leu Ile Tyr Ala Gln Phe Phe Pro Gln Gly Asp Ala Thr
        115                 120                 125

acc tat gca cac ttc ctc ttc aac gcc ttt gat gcg gac ggg aac ggg   432
Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly
    130                 135                 140
```

```
gcc atc cac ttt gag gac ttt gtg gtt ggc ctc tcc atc ctg ctg cgg    480
Ala Ile His Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg
145                 150                 155                 160

ggc aca gtc cac gag aag ctc aag tgg gcc ttt aat ctc tac gac att    528
Gly Thr Val His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile
                165                 170                 175

aac aag gat ggc tac atc acc aaa gag gag atg ctg gcc atc atg aag    576
Asn Lys Asp Gly Tyr Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys
            180                 185                 190

tcc atc tat gac atg atg ggc cgc cac acc tac ccc atc ctg cgg gag    624
Ser Ile Tyr Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu
        195                 200                 205

gac gcg ccg gcg gag cac gtg gag agg ttc ttc gag aaa atg gac cgg    672
Asp Ala Pro Ala Glu His Val Glu Arg Phe Phe Glu Lys Met Asp Arg
    210                 215                 220

aac cag gat ggg gta gtg acc att gaa gag ttc ctg gag gcc tgt cag    720
Asn Gln Asp Gly Val Val Thr Ile Glu Glu Phe Leu Glu Ala Cys Gln
225                 230                 235                 240

aag gat gag aac atc atg agc tcc atg cag ctg ttt gag aat gtc atc    768
Lys Asp Glu Asn Ile Met Ser Ser Met Gln Leu Phe Glu Asn Val Ile
                245                 250                 255

taggacacgt ccaaaggagt gcatggccac agccacctcc acccccaaga aacctccatc 828

ctgccaggag cagcctccaa gaaactttta aaaaatagat ttgcaaaaag tgaacagatt 888

gctacacaca cacacacaca cacacacaca cacacacaca cacagccatt catctgggct 948

ggcagagggg acagagttca gggaggggct gagtctggct aggggccgag tccaggagcc 1008

ccagccagcc cttcccaggc cagcgaggcg aggctgcctc tgggtgagtg gctgacagag 1068

caggtctgca ggccaccagc tgctggatgt caccaagaag ggctcgagt gcccctgcag 1128

gggagggtcc aatctccggt gtgagcccac ctcgtcccgt tctccattct gctttcttgc 1188

cacacagtgg gccggcccca ggctcccctg gtctcctccc cgtagccact ctctgcccac 1248

tacctatgct tctagaaagc ccctcacctc aggaccccag agggaccagc tggggggcag 1308

gggggagagg gggtaatgga ggccaagcct gcagctttct ggaaattctt ccctgggggt 1368

cccaggatcc cctgctactc cactgacctg gaagagctgg gtaccaggcc acccactgtg 1428

gggcaagcct gagtggtgag gggccactgg gccccattct ccctccatgg caggaaggcg 1488

ggggatttca agtttaggga ttgggtcgtg gtggagaatc tgagggcact ctctgccagc 1548

tccacagggt gggatgagcc tctccttgcc ccagtcctgg ttcagtggga atgcagtggg 1608

tggggctgta cacaccctcc agcacagact gttccctcca aggtcctctt aggtcccggg 1668

aggaacgtgg ttcagagact ggcagccagg gagcccgggg cagagctcag aggagtctgg 1728
```

gaaggggcgt gtccctcctc ttcctgtagt gcccctccca tggcccagca gcttggctga 1788

gcccccctct ctgaagcagt gtcgccgtcc ctctgccttg cacaaaaagc acaagcattc 1848

cttagcagct caggcgcagc cctagtggga gcccagcaca ctgcttctcg gaggccaggc 1908

cctcctgctg gctgaggctt gggcccagta gccccaatat ggtggccctg gggaagaggc 1968

cttgggggtc tgctctgtgc ctgggatcag tggggcccca aagcccagcc cggctgacca 2028

acattcaaaa gcacaaaccc tggggactct gcttggctgt cccctccatc tggggatgga 2088

gaatgccagc ccaaagctgg agccaatggt gagggctgag agggctgtgg ctgggtggtc 2148

agcagaaacc cccaggagga gagagatgct gctcccgcct gattggggcc tcacccagaa 2208

ggaacccggt cccaggccgc atggcccctc caggaacatt cccacataat acattccatc 2268

acagccagcc cagctccact cagggctggc ccggggagtc cccgtgtgcc ccaagaggct 2328

agccccaggg tgagcagggc cctcagagga aaggcagtat ggcggaggcc atggggccc 2388

ctcggcattc acacacagcc tggcctcccc tgcggagctg catggacgcc tggctccagg 2448

ctccaggctg actgggggcc tctgcctcca ggagggcatc agctttccct ggctcaggga 2508

tcttctccct cccctcaccc gctgcccagc cctcccagct ggtgtcactc tgcctctaag 2568

gccaaggcct caggagagca tcaccaccac acccctgccg gccttggcct tggggccaga 2628

ctggctgcac agcccaacca ggaggggtct gcctcccacg ctgggacaca gaccggccgc 2688

atgtctgcat ggcagaagcg tctcccttgg ccacggcctg ggagggtggt tcctgttctc 2748

agcatccact aatattcagt cctgtatatt ttaataaaat aaacttgaca aaggaaaaaa 2808

aaaaaaaaaa aattcctgcg gccgcgttct cca 2841

<210> 32
<211> 256
<212> PRT
<213> Homo sapiens

<400> 32
Met Gln Pro Ala Lys Glu Val Thr Lys Ala Ser Asp Gly Ser Leu Leu
1 5 10 15

Gly Asp Leu Gly His Thr Pro Leu Ser Lys Lys Glu Gly Ile Lys Trp
20 25 30

Gln Arg Pro Arg Leu Ser Arg Gln Ala Leu Met Arg Cys Cys Leu Val
35 40 45

Lys Trp Ile Leu Ser Ser Thr Ala Pro Gln Gly Ser Asp Ser Ser Asp
50 55 60

Ser Glu Leu Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp
65 70 75 80

```
Gln Leu Gln Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu
                85                  90                  95

Tyr Arg Gly Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp
            100                 105                 110

Thr Phe Lys Leu Ile Tyr Ala Gln Phe Phe Pro Gln Gly Asp Ala Thr
        115                 120                 125

Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly
    130                 135                 140

Ala Ile His Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg
145                 150                 155                 160

Gly Thr Val His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile
                165                 170                 175

Asn Lys Asp Gly Tyr Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys
            180                 185                 190

Ser Ile Tyr Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu
        195                 200                 205

Asp Ala Pro Ala Glu His Val Glu Arg Phe Phe Glu Lys Met Asp Arg
    210                 215                 220

Asn Gln Asp Gly Val Val Thr Ile Glu Glu Phe Leu Glu Ala Cys Gln
225                 230                 235                 240

Lys Asp Glu Asn Ile Met Ser Ser Met Gln Leu Phe Glu Asn Val Ile
                245                 250                 255


<210> 33
<211> 442
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (1)..(327)

<400> 33
ttt gag gac ttt gtg gtt ggg ctc tcc atc ctg ctt cga ggg acc gtc      48
Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg Gly Thr Val
 1               5                  10                  15

cat gag aag ctc aag tgg gcc ttc aat ctc tac gac atc aac aag gac      96
His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp
            20                  25                  30

ggt tac atc acc aaa gag gag atg ctg gcc atc atg aag tcc atc tac     144
Gly Tyr Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys Ser Ile Tyr
        35                  40                  45

gac atg atg ggc cgc cac acc tac cct atc ctg cgg gag gac gca cct     192
Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu Asp Ala Pro
    50                  55                  60
```

```
ctg gag cat gtg gag agg ttc ttc cag aaa atg gac agg aac cag gat   240
Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg Asn Gln Asp
 65                  70                  75                  80

gga gta gtg act att gat gaa ttt ctg gag act tgt cag aag gac gag   288
Gly Val Val Thr Ile Asp Glu Phe Leu Glu Thr Cys Gln Lys Asp Glu
                85                  90                  95

aac atc atg agc tcc atg cag ctg ttt gag aac gtc atc taggacatgt    337
Asn Ile Met Ser Ser Met Gln Leu Phe Glu Asn Val Ile
            100                 105

aggaggggac cctgggtggc catgggttct caacccagag aagcctcaat cctgacagga 397

gaagcctcta tgagaaacat ttttctaata tatttgcaaa aagtg                 442


<210> 34
<211> 109
<212> PRT
<213> Rattus sp.

<400> 34
Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg Gly Thr Val
  1               5                  10                  15

His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp
            20                  25                  30

Gly Tyr Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys Ser Ile Tyr
        35                  40                  45

Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu Asp Ala Pro
    50                  55                  60

Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg Asn Gln Asp
 65                  70                  75                  80

Gly Val Val Thr Ile Asp Glu Phe Leu Glu Thr Cys Gln Lys Asp Glu
                85                  90                  95

Asn Ile Met Ser Ser Met Gln Leu Phe Glu Asn Val Ile
            100                 105


<210> 35
<211> 2644
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (49)..(816)



<400> 35
cgggctgcaa agcgggaaga ttagtgacgg tccctttcag cagcagag atg cag agg  57
                                                      Met Gln Arg
                                                        1
```

```
acc aag gaa gcc gtg aag gca tca gat ggc aac ctc ctg gga gat cct   105
Thr Lys Glu Ala Val Lys Ala Ser Asp Gly Asn Leu Leu Gly Asp Pro
  5                  10                  15

ggg cgc ata cca ctg agc aag agg gaa agc atc aag tgg caa agg cca   153
Gly Arg Ile Pro Leu Ser Lys Arg Glu Ser Ile Lys Trp Gln Arg Pro
 20                  25                  30                  35

cgg ttc acc cgc cag gcc ctg atg cgt tgc tgc tta atc aag tgg atc   201
Arg Phe Thr Arg Gln Ala Leu Met Arg Cys Cys Leu Ile Lys Trp Ile
                 40                  45                  50

ctg tcc agt gct gcc cca caa ggc tca gac agc agt gac agt gaa ctg   249
Leu Ser Ser Ala Ala Pro Gln Gly Ser Asp Ser Ser Asp Ser Glu Leu
             55                  60                  65

gag tta tcc acg gtg cgc cat cag cca gag ggc ttg gac cag cta caa   297
Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp Gln Leu Gln
         70                  75                  80

gct cag acc aag ttc acc aag aag gag ctg cag tcc ctt tac cga ggc   345
Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu Tyr Arg Gly
     85                  90                  95

ttc aag aat gag tgt ccc aca ggc ctg gtg gat gaa gac acc ttc aaa   393
Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp Thr Phe Lys
100                 105                 110                 115

ctc att tat tcc cag ttc ttc cct cag gga gat gcc acc acc tat gca   441
Leu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ala Thr Thr Tyr Ala
                120                 125                 130

cac ttc ctc ttc aat gcc ttt gat gct gat ggg aac ggg gcc atc cac   489
His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly Ala Ile His
            135                 140                 145

ttt gag gac ttt gtg gtt ggg ctc tcc atc ctg ctt cga ggg acg gtc   537
Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg Gly Thr Val
        150                 155                 160

cat gag aag ctc aag tgg gcc ttc aat ctc tat gac att aac aag gat   585
His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp
    165                 170                 175

ggt tgc atc acc aag gag gag atg ctg gcc atc atg aag tcc atc tac   633
Gly Cys Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys Ser Ile Tyr
180                 185                 190                 195

gac atg atg ggc cgc cac acc tac ccc atc ctg cgg gag gat gca ccc   681
Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu Asp Ala Pro
                200                 205                 210

ctg gag cat gtg gag agg ttc ttt cag aaa atg gac agg aac cag gat   729
Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg Asn Gln Asp
            215                 220                 225

gga gtg gtg acc att gat gaa ttt ctg gag act tgt cag aag gat gag   777
Gly Val Val Thr Ile Asp Glu Phe Leu Glu Thr Cys Gln Lys Asp Glu
        230                 235                 240
```

```
aac atc atg aac tcc atg cag ctg ttt gag aac gtc atc taggacatgt    826
Asn Ile Met Asn Ser Met Gln Leu Phe Glu Asn Val Ile
    245                 250                 255

gggaggggac cccagtggtc attgcttctc aacccagaga agcctcaatc ctgacaggag 886

aagcctctat gagaaacatt tttctaatat atttgcaaaa agtgagcagt ttacttccaa 946

gacacagcca ccgtcacaca cagacacaga catacagaca cacacacaca cacacacaca 1006

tggttcctct ggcttggcca aggaagtggc agccagaagg caccccgcc tattcctagg 1066

tcaataaaaa aggctgcctc tgggatggcc agccctggct agatgttacc cacaaggaac 1126

tcagagatcg agaggaccag gtctacaaag ctaaggtccc tgtgtctttt ctaccactcg 1186

ggagatcaaa ctactccctg cctatggacc catgctctta ggaagctccc agaaactcca 1246

aggggacaaa gaggggagag gtctatagga agaaatggtt ttggaagctg ggcttgcagc 1306

cttatgctaa tgatcacctg gggtcctgga acccgagtgc caggctacct actatgccgt 1366

gagcttagat agtgaggggc cattggacta agacctcctg taagagtggg gcaggattga 1426

ggtttttgga gaaactgagg aaacaatttg tccataccac tgggtgaaga ctgctggcca 1486

gtgggaatgt ggctggtgga gatttcccaa cttccagcac caggatggcc tctccaaggt 1546

cctctttgat tccctgggga gatcacctgg ctcatagact gacaaccagg gaactgggct 1606

gaaatgggag gtctggtagg gggcatcccc ctccttttcc ctggccactt gccacccagt 1666

tccttaacac agtggatcgg ccacacctct gtggctgccc ttgaacagac tcatcccgac 1726

caagacaaaa aagcacaaac tcctagcagc tcaggccaag cccacaaggg aaggcctggg 1786

tccctgcagc cctgattcag tggccgagga agacgctcag acatccatcc tgtacctcgg 1846

agccttgggg gtctcacagc cctttcccag cccagctcgc caacattcta aagcacaaac 1906

ctgcggattc tgcttgcttg ggctgcgccc tggggattga aggccactgt taaccctaag 1966

ctggagctag ccctgagggc tggggacctg tgaccaggca acaggtcagc agaccctcag 2026

gaggagagag agctgttcct gcctccccag gcctcgccca gaaggaacag tgtcccaaga 2086

agcatgtttc ctggaggaac atccccacaa aagtacattc catcatctga agcccggtct 2146

ctgctcaggc ctgcctctga aagtccacgt gtgttcccca gaaggccagc cccaagataa 2206

gggaggtcct tagaggaagg acagggtgac aacaccccta tacacaggtg gacccccct 2266

ctgaggactg tactgacccc atctccatcc tgaccggggc cttcctttac ccgatctaca 2326

gaccaccagt tctccctggc tcagggaccc cctgtccccc agtctgactc ttcccatcga 2386

ggtccctgtc ttgtgaaaag ccaaggccac gggaaaaggc caccactcta acctgctgca 2446

tcccttagcc tctggctgca cgcccaacct ggaggggtct gtccccttg cagggacaca 2506

gactggccgc atgtccgcat ggcagaagcg tctcccttgg gtgcagcctg gaagggtggt 2566
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ttctgtctca gcgcccacca atattcagtc ctatatattt taataaaaga aacttgacaa 2626

aggaaaaaaa aaaaaaaa 2644

<210> 36
<211> 256
<212> PRT
<213> Mus musculus

<400> 36

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Met Gln Arg Thr Lys Glu Ala Val Lys Ala Ser Asp Gly Asn Leu Leu
  1               5                  10                  15

Gly Asp Pro Gly Arg Ile Pro Leu Ser Lys Arg Glu Ser Ile Lys Trp
            20                  25                  30

Gln Arg Pro Arg Phe Thr Arg Gln Ala Leu Met Arg Cys Cys Leu Ile
        35                  40                  45

Lys Trp Ile Leu Ser Ser Ala Ala Pro Gln Gly Ser Asp Ser Ser Asp
    50                  55                  60

Ser Glu Leu Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp
65                  70                  75                  80

Gln Leu Gln Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu
                85                  90                  95

Tyr Arg Gly Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp
            100                 105                 110

Thr Phe Lys Leu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ala Thr
        115                 120                 125

Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly
    130                 135                 140

Ala Ile His Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg
145                 150                 155                 160

Gly Thr Val His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile
                165                 170                 175

Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys
            180                 185                 190

Ser Ile Tyr Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu
        195                 200                 205

Asp Ala Pro Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg
    210                 215                 220

Asn Gln Asp Gly Val Val Thr Ile Asp Glu Phe Leu Glu Thr Cys Gln
225                 230                 235                 240

Lys Asp Glu Asn Ile Met Asn Ser Met Gln Leu Phe Glu Asn Val Ile
                245                 250                 255
```

<210> 37
<211> 531
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(336)

<220>
<223> At position 495, n=any amino acid

<400> 37
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cac gag gtg gaa agc att tcg gct cag ctg gag gag gcc agc tct aca   48
His Glu Val Glu Ser Ile Ser Ala Gln Leu Glu Glu Ala Ser Ser Thr
  1               5                  10                  15

ggc ggt ttc ctg tac gct cag aac agc acc aag cgc agc att aaa gag   96
Gly Gly Phe Leu Tyr Ala Gln Asn Ser Thr Lys Arg Ser Ile Lys Glu
             20                  25                  30

cgg ctc atg aag ctc ttg ccc tgc tca gct gcc aaa acg tcg tct cct   144
Arg Leu Met Lys Leu Leu Pro Cys Ser Ala Ala Lys Thr Ser Ser Pro
         35                  40                  45

gct att caa aac agc gtg gaa gat gaa ctg gag atg gcc acc gtc agg   192
Ala Ile Gln Asn Ser Val Glu Asp Glu Leu Glu Met Ala Thr Val Arg
     50                  55                  60

cat cgg ccc gaa gcc ctt gag ctt ctg gaa gcc cag agc aaa ttt acc   240
His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys Phe Thr
 65                  70                  75                  80

aag aaa gag ctt cag atc ctt tac aga gga ttt aag aac gta aga act   288
Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Val Arg Thr
                 85                  90                  95

ttc ttt ttg act tta cct tca cac aat tcc cag agg agc att gag aaa   336
Phe Phe Leu Thr Leu Pro Ser His Asn Ser Gln Arg Ser Ile Glu Lys
            100                 105                 110

tgagaggaaa aggggaaaa tatcccattc tatgagaagc cccatcatat gtatatttca 396

tactgatcct tcccagatag gaatataatc agtatctgtg gactttgaat ctctgtggca 456

cacccatgct ggcatactgt aattgcccat taaacaaana gtttttgaga aaaaaaaaaa 516

aaaaaaaaaa aaaaa                                                  531
```

<210> 38
<211> 112
<212> PRT
<213> Homo sapiens

<400> 38
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His Glu Val Glu Ser Ile Ser Ala Gln Leu Glu Glu Ala Ser Ser Thr
  1               5                  10                  15

Gly Gly Phe Leu Tyr Ala Gln Asn Ser Thr Lys Arg Ser Ile Lys Glu
             20                  25                  30
```

```
Arg Leu Met Lys Leu Leu Pro Cys Ser Ala Ala Lys Thr Ser Ser Pro
         35                  40                  45

Ala Ile Gln Asn Ser Val Glu Asp Glu Leu Glu Met Ala Thr Val Arg
     50                  55                  60

His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys Phe Thr
 65                  70                  75                  80

Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Val Arg Thr
                 85                  90                  95

Phe Phe Leu Thr Leu Pro Ser His Asn Ser Gln Arg Ser Ile Glu Lys
            100                 105                 110
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<210> 39
<211> 2176
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (2)..(124)

<400> 39

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t gaa agg ttc ttc gag aaa atg gac cgg aac cag gat ggg gta gtg acc 49
  Glu Arg Phe Phe Glu Lys Met Asp Arg Asn Gln Asp Gly Val Val Thr
    1               5                  10                  15

att gaa gag ttc ctg gag gcc tgt cag aag gat gag aac atc atg agc   97
Ile Glu Glu Phe Leu Glu Ala Cys Gln Lys Asp Glu Asn Ile Met Ser
            20                  25                  30

tcc atg cag ctg ttt gag aat gtc atc taggacacgt ccaaaggagt         144
Ser Met Gln Leu Phe Glu Asn Val Ile
        35                  40
```

gcatggccac agccacctcc acccccaaga aacctccatc ctgccaggag cagcctccaa 204

gaaactttta aaaaatagat ttgcaaaaag tgaacagatt gctacacaca cacacacaca 264

cacacacaca cacacacaca cacagccatt catctgggct ggcagagggg acagagttca 324

gggaggggct gagtctggct aggggccgag tccaggagcc ccagccagcc cttcccaggc 384

cagcgaggcg aggctgcctc tgggtgagtg gctgacagag caggtctgca ggccaccagc 444

tgctggatgt caccaagaag gggctcgagt gcccctgcag gggagggtcc aatctccggt 504

gtgagcccac ctcgtcccgt tctccattct gctttcttgc cacacagtgg gccggcccca 564

ggctcccctg gtctcctccc cgtagccact ctctgcccac tacctatgct tctagaaagc 624

ccctcacctc aggaccccag agggaccagc tgggggggcag gggggagagg gggtaatgga 684

ggccaagcct gcagctttct ggaaattctt ccctgggggt cccaggatcc cctgctactc 744

cactgacctg gaagagctgg gtaccaggcc acccactgtg gggcaagcct gagtggtgag 804

gggccactgg gccccattct ccctccatgg caggaaggcg ggggatttca agtttaggga 864

ttgggtcgtg gtggagaatc tgagggcact ctctgccagc tccacagggt gggatgagcc 924

tctccttgcc ccagtcctgg ttcagtggga atgcagtggg tggggctgta cacaccctcc 984

agcacagact gttccctcca aggtcctctt aggtcccggg aggaacgtgg ttcagagact 1044

ggcagccagg gagcccgggg cagagctcag aggagtctgg gaaggggcgt gtccctcctc 1104

ttcctgtagt gcccctccca tggcccagca gcttggctga gcccctctc ctgaagcagt 1164

gtcgccgtcc ctctgccttg cacaaaaagc acaagcattc cttagcagct caggcgcagc 1224

cctagtggga gcccagcaca ctgcttctcg gaggccaggc cctcctgctg gctgaggctt 1284

gggcccagta gccccaatat ggtggccctg gggaagaggc cttgggggtc tgctctgtgc 1344

ctgggatcag tggggcccca aagcccagcc cggctgacca acattcaaaa gcacaaaccc 1404

tggggactct gcttggctgt cccctccatc tggggatgga gaatgccagc ccaaagctgg 1464

agccaatggt gagggctgag agggctgtgg ctgggtggtc agcagaaacc cccaggagga 1524

gagagatgct gctcccgcct gattggggcc tcacccagaa ggaacccggt cccaggccgc 1584

atggcccctc caggaacatt cccacataat acattccatc acagccagcc cagctccact 1644

cagggctggc ccggggagtc cccgtgtgcc ccaagaggct agccccaggg tgagcagggc 1704

cctcagagga aaggcagtat ggcggaggcc atgggggccc ctcggcattc acacacagcc 1764

tggcctcccc tgcggagctg catggacgcc tggctccagg ctccaggctg actgggggcc 1824

tctgcctcca ggagggcatc agctttccct ggctcaggga tcttctccct cccctcaccc 1884

gctgcccagc cctcccagct ggtgtcactc tgcctctaag gccaaggcct caggagagca 1944

tcaccaccac acccctgccg gccttggcct tggggccaga ctggctgcac agcccaacca 2004

ggaggggtct gcctcccacg ctgggacaca gaccggccgc atgtctgcat ggcagaagcg 2064

tctcccttgg ccacggcctg ggagggtggt tcctgttctc agcatccact aatattcagt 2124

cctgtatatt ttaataaaat aaacttgaca aaggaaaaaa aaaaaaaaaa aa 2176

<210> 40
<211> 41
<212> PRT
<213> Homo sapiens

<400> 40
Glu Arg Phe Phe Glu Lys Met Asp Arg Asn Gln Asp Gly Val Val Thr
1 5 10 15

Ile Glu Glu Phe Leu Glu Ala Cys Gln Lys Asp Glu Asn Ile Met Ser
20 25 30

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Ser Met Gln Leu Phe Glu Asn Val Ile
         35                  40


<210> 41
<211> 2057
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (208)..(963)

<400> 41
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tctctaaaga aaagccttgc cagcccctac tcccggcccc caaccccagc aggtcgctgc 120

gccgccaggg ggcgctgtgt gagcgcccta ttctggccac ccggcgcccc ctcccacggc 180

ccaggcggga gcggggcgcc gggggcc atg cgg ggc caa ggc aga aag gag agt 234
                              Met Arg Gly Gln Gly Arg Lys Glu Ser
                                1               5

ttg tcc gaa tcc cga gat ctg gac ggc tcc tat gac cag ctt acg ggc   282
Leu Ser Glu Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly
 10                  15                  20                  25


cac cct cca ggg ccc agt aaa aaa gcc ctg aag cag cgt ttc ctc aag   330
His Pro Pro Gly Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys
                 30                  35                  40

ctg ctg ccg tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aac   378
Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Asn
             45                  50                  55

agc gta gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag   426
Ser Val Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu
         60                  65                  70

ggc ctg gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg   474
Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu
     75                  80                  85

cag gtc ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc   522
Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val
 90                  95                 100                 105

aac gag gag aac ttc aag cag att tat tct cag ttc ttt ccc caa gga   570
Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly
                110                 115                 120

gac tcc agc aac tat gct act ttt ctc ttc aat gcc ttt gac acc aac   618
Asp Ser Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn
            125                 130                 135

cac gat ggc tct gtc agt ttt gag gac ttt gtg gct ggt ttg tcg gtg   666
His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val
        140                 145                 150
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att ctt cgg ggg acc ata gat gat aga ctg agc tgg gct ttc aac tta   714
Ile Leu Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu
    155                 160                 165

tat gac ctc aac aag gac ggc tgt atc aca aag gag gaa atg ctt gac   762
Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp
170                 175                 180                 185

att atg aag tcc atc tat gac atg atg ggc aag tac aca tac cct gcc   810
Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala
                190                 195                 200

ctc cgg gag gag gcc cca aga gaa cac gtg gag agc ttc ttc cag aag   858
Leu Arg Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys
            205                 210                 215

atg gac agg aac aag gac ggc gtg gtg acc atc gag gaa ttc atc gag   906
Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu
        220                 225                 230

tct tgt caa cag gac gag aac atc atg agg tcc atg cag ctc tca ccc   954
Ser Cys Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Ser Pro
    235                 240                 245


ctt ctc aac tgatacctag tgctgaggac acccctggtg tagggaccaa           1003
Leu Leu Asn
250

gtggttctcc accttctagt cccactctag aaaccacatt agacagaagg tctcctgcta 1063

tggtgctttc cccatcccta atctcttaga ttttcctcaa gactcccttc tcagagaaca 1123

cgctctgtcc atgtccccag ctggcttctc agcctagcct ttgagggccc tgtggggagg 1183

cggggacaag aaagcagaaa agtcttggcc ccgagccagt ggttaggtcc taggaattgg 1243

ctggagtgga ggccagaaag cctgggcaga tgatgagagc ccagctgggc tgtcactgca 1303

ggttccgggg cctacagccc tgggtcagca gagtatgagt tcccagactt tccagaaggt 1363

ccttagcaat gtcccagaaa ttcaccgtac acttctcagt gtcttaggag ggcccgggat 1423

ccagatgtct ggttcatccc tgaatcctct ccctccttct tgctcgtatg gtgggagtgg 1483

tggccagggg aagatgagtg gtgtcccgga tgatgcctgt caaggtccca cctcccctcc 1543

ggctgttctc atgacagctg tttggttctc catgacccct atctagatgt agaggcatgg 1603

agtgagtcag ggatttcccg aacttgagtt ttaccactcc tcctagtggc tgccttaggg 1663

gaatgggaag aacccagtgt gggggcaccc attagaatct ttgcccggct cctcacaatg 1723

ccctagggtc ccctagggta cccgctccct ctgtttagtc tacccagaga tgctcctgag 1783

ctcacctaga gggtagggac ggtaggctcc aggtccaacc tctccaggtc agcaccctgc 1843

catgctgctg ctcctcatta acaaacctgc ttgtctcctc ctgcgcccct tctcagtcag 1903

ccagggtctg aggggaaggg cctcccgttt ccccatccgt cagacatggt tgactgcttt 1963
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gcattttggg ctcttctatc tattttgtaa aataagacat cagatccaat aaaacacacg 2023

gctatgcaca aaaaaaaaaa aaaaaaaaaa aaaa 2057

<210> 42
<211> 252
<212> PRT
<213> Rattus sp.

<400> 42
Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Glu Ser Arg Asp Leu
1 5 10 15

Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly Pro Ser Lys
20 25 30

Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
35 40 45

Gln Ala Leu Pro Ser Val Ser Glu Asn Ser Val Glu Asp Glu Phe Glu
50 55 60

Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
65 70 75 80

Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe
85 90 95

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
100 105 110

Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr Ala Thr
115 120 125

Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
130 135 140

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Ile Asp
145 150 155 160

Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
165 170 175

Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
180 185 190

Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
195 200 205

Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
210 215 220

Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Gln Asp Glu Asn
225 230 235 240

Ile Met Arg Ser Met Gln Leu Ser Pro Leu Leu Asn
245 250

<210> 43
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Xaas at positions 2,5,6,9,17,25 and 26 may be Ile, Leu, Val or Met

<220>
<223> Xaas at positions 3,4,7,8,16,18-20,23 and 24 may be any amino acid

<220>
<223> Description of Artificial Sequence: consensus motif

<400> 43
Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Lys Asp Gly Asp Gly Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Glu Phe Xaa Xaa Xaa Xaa
20 25

<210> 44
<211> 40
<212> DNA
<213> Rattus sp.

<400> 44
taatacgact cactataggg actggccatc ctgctctcag 40

<210> 45
<211> 40
<212> DNA
<213> Rattus sp.

<400> 45
attaaccctc actaaaggga cactactgtt taagctcaag 40

<210> 46
<211> 40
<212> DNA
<213> Rattus sp.

<400> 46
taatacgact cactataggg cacctcccct ccggctgttc 40

<210> 47
<211> 40
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<213> Rattus sp.

<400> 47
attaaccctc actaaaggga gagcagcagc atggcagggt 40

<210> 48
<211> 2413
<212> DNA
<213> Simian sp.

<220>
<221> CDS
<222> (265)..(963)

<400> 48
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ggatcagcat gagaggctgg actttagtcc aggtctgtcc tcaccccggg ggaccgccgg 120

ctttgcaggg tgcagctgcg aggaactgct cacttttttc cccttgcaag tctttgttcc 180

aagcctgacg ttgctacgat tctgtaatta actccctcca ctccaaaggg gtctggaggc 240

tgggatgctc tgccagctca gagg atg ttg act ctg gag tgg gag tcc gaa 291
Met Leu Thr Leu Glu Trp Glu Ser Glu
1 5

gga ctg caa aca gtg ggt att gtt gtg att ata tgt gca tct ctg aag 339
Gly Leu Gln Thr Val Gly Ile Val Val Ile Ile Cys Ala Ser Leu Lys
10 15 20 25

ctg ctt cat ttg ctg gga ctg att gat ttt tcg gaa gac agc gtg gaa 387
Leu Leu His Leu Leu Gly Leu Ile Asp Phe Ser Glu Asp Ser Val Glu
30 35 40

gat gaa ctg gag atg gcc act gtc agg cat cgg cct gag gcc ctt gag 435
Asp Glu Leu Glu Met Ala Thr Val Arg His Arg Pro Glu Ala Leu Glu
45 50 55

ctt ctg gaa gcc cag agc aaa ttt acc aag aaa gag ctt cag atc ctt 483
Leu Leu Glu Ala Gln Ser Lys Phe Thr Lys Lys Glu Leu Gln Ile Leu
60 65 70

tac aga gga ttt aag aac gaa tgc ccc agt ggt gtt gtt aat gaa gaa 531
Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val Val Asn Glu Glu
75 80 85

acc ttc aaa gag att tac tcg cag ttc ttt cca cag gga gac tct aca 579
Thr Phe Lys Glu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Thr
90 95 100 105

aca tat gca cat ttt ctg ttc aat gcg ttt gat acg gac cac aat gga 627
Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Thr Asp His Asn Gly
110 115 120

gct gtg agt ttc gag gat ttc atc aaa ggt ctt tcc att ttg ctc cgg 675
Ala Val Ser Phe Glu Asp Phe Ile Lys Gly Leu Ser Ile Leu Leu Arg
125 130 135

ggg aca gta caa gaa aaa ctc aat tgg gca ttt aat ctg tat gat ata 723
Gly Thr Val Gln Glu Lys Leu Asn Trp Ala Phe Asn Leu Tyr Asp Ile
140 145 150

aat aaa gat ggc tac atc act aaa gag gaa atg ctt gat ata atg aaa 771
Asn Lys Asp Gly Tyr Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys
155 160 165

gca ata tac gac atg atg ggt aaa tgt aca tat cct gtc ctc aaa gaa 819
Ala Ile Tyr Asp Met Met Gly Lys Cys Thr Tyr Pro Val Leu Lys Glu
170 175 180 185

gat gca ccc aga caa cac gtc gaa aca ttt ttt cag aaa atg gac aaa 867
Asp Ala Pro Arg Gln His Val Glu Thr Phe Phe Gln Lys Met Asp Lys
190 195 200

aat aaa gat ggg gtt gtt acc ata gat gag ttc att gaa agc tgc caa 915
Asn Lys Asp Gly Val Val Thr Ile Asp Glu Phe Ile Glu Ser Cys Gln
205 210 215

aaa gat gaa aac ata atg cgc tcc atg cag ctc ttt gaa aat gtg att 963
Lys Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Glu Asn Val Ile
220 225 230

taacttgtca actagatcct gaatccaaca gacaaatgtg aactattcta ccacccttaa 1023

agtcggagct accactttta gcatagattg ctcagcttga cactgaagca tattatgcaa 1083

acaagctttg ttttaatata aagcaatccc caaaagattt gagtttctca gttataaatt 1143

tgcatccttt ccataatgcc actgagttca tgggatgttc taactcattt catactctgt 1203

gaatattcaa aagtaataga atctggcata tagttttatt gattccttag ccatgggatt 1263

attgaggctt tcacatatca gtgattttaa aataccagtg tttttgctc tcatttgtat 1323

gtattcagtc ctaggatttt gaatggtttt ctaatatact gacatctgca tttaatttcc 1383

agaaattaaa ttaattttca tgtctgaatg ctgtaattcc atttatatac tttaagtaaa 1443

caaataagat tactacaatt aaacacatag ttccagtttc tatggccttc ccttcccacc 1503

ttctattata aattaatttt atctggtatt tttaaacatt taaaaattta tcatcagata 1563

tcagcatatg cctaattatg cctaatgaaa cttaataagc atttaatttt ccatcataca 1623

ttatagccaa ggcctatata ctatatataa ttttggattt gtttaatctt acaggctgtt 1683

ttccattgta tcatcaagtg gaagttcaag acggcatcaa acaaaacaag gatgtttaca 1743

gacatatgca aagggtcagg atatctatcc tccagtatat gttaatgctt aataacaagt 1803

aatcctaaca gcattaaagg ccaaatctgt cctctttccc ctgacttcct tacagcatgt 1863

ttatattaca agccattcag ggacaaagaa accttgacta ccccactgtc tactaggaac 1923

aaacaaacag caagcaaaat tcactttgaa agcaccagtg gttccattac attgacaact 1983

actaccaaga ttcagtagaa aataagtgct caacaactaa tccagattac aatatgattt 2043

agtgcatcat aaaattccaa caattcagat tatttttaat catctcagcc acaactgtaa 2103

agttgccaca ttactaaaga cacacacatc gtccctgttt tgtagaaata tcacaaagac 2163

caagaggcta cagaaggagg aaatttgcaa ctgtctttgc aacaataaat caggtatcta 2223

ttctggtgta gagataggat gttgaaagct gccctgctat caccagtgta gaaattaaga 2283

gtagtacaat acatgtacac tgaaatttgc catcgcgtgt ttgtgtaaac tcaatgtgca 2343

cattttgtat ttcaaaaaga aaaaataaaa gcaaaataaa atgttwawaa mwmwaaaaaa 2403

aaaaaaaaaa 2413

<210> 49
<211> 233
<212> PRT
<213> Simian sp.

<400> 49

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Met Leu Thr Leu Glu Trp Glu Ser Glu Gly Leu Gln Thr Val Gly Ile
  1               5                  10                  15

Val Val Ile Ile Cys Ala Ser Leu Lys Leu Leu His Leu Leu Gly Leu
            20                  25                  30

Ile Asp Phe Ser Glu Asp Ser Val Glu Asp Glu Leu Glu Met Ala Thr
        35                  40                  45

Val Arg His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys
    50                  55                  60

Phe Thr Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Glu
65                  70                  75                  80

Cys Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Glu Ile Tyr Ser
                85                  90                  95

Gln Phe Phe Pro Gln Gly Asp Ser Thr Thr Tyr Ala His Phe Leu Phe
            100                 105                 110

Asn Ala Phe Asp Thr Asp His Asn Gly Ala Val Ser Phe Glu Asp Phe
        115                 120                 125

Ile Lys Gly Leu Ser Ile Leu Leu Arg Gly Thr Val Gln Glu Lys Leu
    130                 135                 140

Asn Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Thr
145                 150                 155                 160

Lys Glu Glu Met Leu Asp Ile Met Lys Ala Ile Tyr Asp Met Met Gly
                165                 170                 175

Lys Cys Thr Tyr Pro Val Leu Lys Glu Asp Ala Pro Arg Gln His Val
            180                 185                 190

Glu Thr Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Val Val Thr
        195                 200                 205

Ile Asp Glu Phe Ile Glu Ser Cys Gln Lys Asp Glu Asn Ile Met Arg
    210                 215                 220

Ser Met Gln Leu Phe Glu Asn Val Ile
225                 230
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<210> 50
<211> 1591
<212> DNA
<213> Simian sp.

<220>
<221> CDS
<222> (265)..(963)

<400> 50
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ggatcagcat gagaggctgg actttagtcc aggtctgtcc tcaccccggg ggaccgccgg 120

ctttgcaggg tgcagctgcg aggaactgct cactttttc cccttgcaag tctttgttcc 180

aagcctgacg ttgctacgat tctgtaatta actccctcca ctccaaaggg gtctggaggc 240

tgggatgctc tgccagctca gagg atg ttg act ctg gag tgg gag tcc gaa 291
Met Leu Thr Leu Glu Trp Glu Ser Glu
1 5

gga ctg caa aca gtg ggt att gtt gtg att ata tgt gca tct ctg aag 339
Gly Leu Gln Thr Val Gly Ile Val Val Ile Ile Cys Ala Ser Leu Lys
10 15 20 25

ctg ctt cat ttg ctg gga ctg att gat ttt tcg gaa gac agc gtg gaa 387
Leu Leu His Leu Leu Gly Leu Ile Asp Phe Ser Glu Asp Ser Val Glu
30 35 40

gat gaa ctg gag atg gcc act gtc agg cat cgg cct gag gcc ctt gag 435
Asp Glu Leu Glu Met Ala Thr Val Arg His Arg Pro Glu Ala Leu Glu
45 50 55

ctt ctg gaa gcc cag agc aaa ttt acc aag aaa gag ctt cag atc ctt 483
Leu Leu Glu Ala Gln Ser Lys Phe Thr Lys Lys Glu Leu Gln Ile Leu
60 65 70

tac aga gga ttt aag aac gaa tgc ccc agt ggt gtt gtt aat gaa gaa 531
Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val Val Asn Glu Glu
75 80 85

acc ttc aaa gag att tac tcg cag ttc ttt cca cag gga gac tct aca 579
Thr Phe Lys Glu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Thr
90 95 100 105

aca tat gca cat ttt ctg ttc aat gcg ttt gat acg gac cac aat gga 627
Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Thr Asp His Asn Gly
110 115 120

gct gtg agt ttc gag gat ttc atc aaa ggt ctt tcc att ttg ctc cgg 675
Ala Val Ser Phe Glu Asp Phe Ile Lys Gly Leu Ser Ile Leu Leu Arg
125 130 135

ggg aca gta caa gaa aaa ctc aat tgg gca ttt aat ctg tat gat ata 723
Gly Thr Val Gln Glu Lys Leu Asn Trp Ala Phe Asn Leu Tyr Asp Ile
140 145 150

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aat aaa gat ggc tac atc act aaa gag gaa atg ctt gat ata atg aaa   771
Asn Lys Asp Gly Tyr Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys
    155                 160                 165

gca ata tac gac atg atg ggt aaa tgt aca tat cct gtc ctc aaa gaa   819
Ala Ile Tyr Asp Met Met Gly Lys Cys Thr Tyr Pro Val Leu Lys Glu
170                 175                 180                 185

gat gca ccc aga caa cac gtc gaa aca ttt ttt cag gct gtt ttc cat   867
Asp Ala Pro Arg Gln His Val Glu Thr Phe Phe Gln Ala Val Phe His
                190                 195                 200

tgt atc atc aag tgg aag ttc aag acg gca tca aac aaa aca agg atg   915
Cys Ile Ile Lys Trp Lys Phe Lys Thr Ala Ser Asn Lys Thr Arg Met
            205                 210                 215

ttt aca gac ata tgc aaa ggg tca gga tat cta tcc tcc agt ata tgt   963
Phe Thr Asp Ile Cys Lys Gly Ser Gly Tyr Leu Ser Ser Ser Ile Cys
        220                 225                 230

taatgcttaa taacaagtaa tcctaacagc attaaaggcc aaatctgtcc tctttcccct 1023

gacttcctta cagcatgttt atattacaag ccattcaggg acaaagaaac cttgactacc 1083

ccactgtcta ctaggaacaa acaaacagca agcaaaattc actttgaaag caccagtggt 1143

tccattacat tgacaactac taccaagatt cagtagaaaa taagtgctca acaactaatc 1203

cagattacaa tatgatttag tgcatcataa aattccaaca attcagatta tttttaatca 1263

tctcagccac aactgtaaag ttgccacatt actaaagaca cacacatcgt ccctgttttg 1323

tagaaatatc acaaagacca agaggctaca gaaggaggaa atttgcaact gtctttgcaa 1383

caataaatca ggtatctatt ctggtgtaga gataggatgt tgaaagctgc cctgctatca 1443

ccagtgtaga aattaagagt agtacaatac atgtacactg aaatttgcca tcgcgtgttt 1503

gtgtaaactc aatgtgcaca ttttgtattt caaaaagaaa aaataaaagc aaaataaaat 1563

gttwawaamw mwaaaaaaaa aaaaaaaa                                    1591
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<210> 51
<211> 233
<212> PRT
<213> Simian sp.

<400> 51

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Met Leu Thr Leu Glu Trp Glu Ser Glu Gly Leu Gln Thr Val Gly Ile
  1               5                  10                  15

Val Val Ile Ile Cys Ala Ser Leu Lys Leu Leu His Leu Leu Gly Leu
             20                  25                  30

Ile Asp Phe Ser Glu Asp Ser Val Glu Asp Glu Leu Glu Met Ala Thr
         35                  40                  45
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Val Arg His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys
      50                  55                  60

Phe Thr Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Glu
 65                  70                  75                  80

Cys Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Glu Ile Tyr Ser
                85                  90                  95

Gln Phe Phe Pro Gln Gly Asp Ser Thr Thr Tyr Ala His Phe Leu Phe
            100                 105                 110

Asn Ala Phe Asp Thr Asp His Asn Gly Ala Val Ser Phe Glu Asp Phe
        115                 120                 125

Ile Lys Gly Leu Ser Ile Leu Leu Arg Gly Thr Val Gln Glu Lys Leu
    130                 135                 140

Asn Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Thr
145                 150                 155                 160

Lys Glu Glu Met Leu Asp Ile Met Lys Ala Ile Tyr Asp Met Met Gly
                165                 170                 175

Lys Cys Thr Tyr Pro Val Leu Lys Glu Asp Ala Pro Arg Gln His Val
            180                 185                 190

Glu Thr Phe Phe Gln Ala Val Phe His Cys Ile Ile Lys Trp Lys Phe
        195                 200                 205

Lys Thr Ala Ser Asn Lys Thr Arg Met Phe Thr Asp Ile Cys Lys Gly
    210                 215                 220

Ser Gly Tyr Leu Ser Ser Ser Ile Cys
225                 230
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<210> 52
<211> 2051
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (85)..(1305)

<400> 52
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tctgcagggc tgtcagctgc caaa atg aac ggc gtg gaa ggg aac aac gag 111
Met Asn Gly Val Glu Gly Asn Asn Glu
1 5

ctc cct ctc gct aac acc tcg acc tcc gcc ctt gtc ccg gaa gat ctg 159
Leu Pro Leu Ala Asn Thr Ser Thr Ser Ala Leu Val Pro Glu Asp Leu
10 15 20 25

gat ctg aag caa gac cag ccg ctc agc gag gaa act gac acg gtg cgg 207
Asp Leu Lys Gln Asp Gln Pro Leu Ser Glu Glu Thr Asp Thr Val Arg
30 35 40

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gag atg gag gct gca ggt gag gcc ggt gcg gag gga ggc gcg tcc ccc   255
Glu Met Glu Ala Ala Gly Glu Ala Gly Ala Glu Gly Gly Ala Ser Pro
                45                  50                  55

gat tcg gag cac tgc gac ccc cag ctc tgc ctc cga gtg gct gag aat   303
Asp Ser Glu His Cys Asp Pro Gln Leu Cys Leu Arg Val Ala Glu Asn
            60                  65                  70

ggc tgt gct gcc gca gcg gga gag ggg ctg gag gat ggt ctg tct tca   351
Gly Cys Ala Ala Ala Ala Gly Glu Gly Leu Glu Asp Gly Leu Ser Ser
        75                  80                  85

tca aag tgt ggg gac gca ccc ttg gcg tct gtg gca gcc aac gac agc   399
Ser Lys Cys Gly Asp Ala Pro Leu Ala Ser Val Ala Ala Asn Asp Ser
    90                  95                  100                 105

aat aaa aat ggc tgt cag ctt gca ggg ccg ctc agc cct gct aag cca   447
Asn Lys Asn Gly Cys Gln Leu Ala Gly Pro Leu Ser Pro Ala Lys Pro
                110                 115                 120

aaa act ctg gaa gcc agt ggt gca gtg ggc ctg ggg tcg cag atg atg   495
Lys Thr Leu Glu Ala Ser Gly Ala Val Gly Leu Gly Ser Gln Met Met
            125                 130                 135

cca ggg ccg aag aag acc aag gta atg act acc aag ggc gcc atc tct   543
Pro Gly Pro Lys Lys Thr Lys Val Met Thr Thr Lys Gly Ala Ile Ser
        140                 145                 150

gcg act aca ggc aag gaa gga gaa gca ggg gcg gca atg cag gaa aag   591
Ala Thr Thr Gly Lys Glu Gly Glu Ala Gly Ala Ala Met Gln Glu Lys
    155                 160                 165

aag ggg gtg cag aaa gaa aaa aag gca gct gga gga ggg aaa gac gag   639
Lys Gly Val Gln Lys Glu Lys Lys Ala Ala Gly Gly Gly Lys Asp Glu
170                 175                 180                 185

act cgt cct aga gcc cct aag atc aat aac tgc atg gac tcc ctg gaa   687
Thr Arg Pro Arg Ala Pro Lys Ile Asn Asn Cys Met Asp Ser Leu Glu
                190                 195                 200

gcc atc gat caa gag ctg tca aat gta aat gcg caa gct gac agg gcc   735
Ala Ile Asp Gln Glu Leu Ser Asn Val Asn Ala Gln Ala Asp Arg Ala
            205                 210                 215

ttc ctc cag ctg gaa cgc aaa ttt ggg cgg atg aga agg ctc cac atg   783
Phe Leu Gln Leu Glu Arg Lys Phe Gly Arg Met Arg Arg Leu His Met
        220                 225                 230


cag cgc cga agt ttc atc atc caa aac atc cca ggt ttc tgg gtc aca   831
Gln Arg Arg Ser Phe Ile Ile Gln Asn Ile Pro Gly Phe Trp Val Thr
    235                 240                 245

gcg ttt cgg aac cac ccg caa ctg tca ccg atg atc agt ggc caa gat   879
Ala Phe Arg Asn His Pro Gln Leu Ser Pro Met Ile Ser Gly Gln Asp
250                 255                 260                 265

gaa gac atg atg agg tac atg atc aat tta gag gtg gag gag ctt aag   927
Glu Asp Met Met Arg Tyr Met Ile Asn Leu Glu Val Glu Glu Leu Lys
                270                 275                 280
```

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cac cca aga gca ggg tgc aaa ttt aag ttc atc ttc caa agc aac ccc   975
His Pro Arg Ala Gly Cys Lys Phe Lys Phe Ile Phe Gln Ser Asn Pro
            285                 290                 295

tac ttc cga aat gag ggg ctg gtc aaa gag tac gag cgc aga tcc tca  1023
Tyr Phe Arg Asn Glu Gly Leu Val Lys Glu Tyr Glu Arg Arg Ser Ser
        300                 305                 310

ggt cga gtg gtg tcg ctc tct acg cca atc cgc tgg cac cgg ggt caa  1071
Gly Arg Val Val Ser Leu Ser Thr Pro Ile Arg Trp His Arg Gly Gln
    315                 320                 325

gaa ccc cag gcc cat atc cac agg aat aga gag ggg aac acg att ccc  1119
Glu Pro Gln Ala His Ile His Arg Asn Arg Glu Gly Asn Thr Ile Pro
330                 335                 340                 345

agt ttc ttc aat tgg ttc tca gac cac agc ctc cta gaa ttc gac aga  1167
Ser Phe Phe Asn Trp Phe Ser Asp His Ser Leu Leu Glu Phe Asp Arg
                350                 355                 360

ata gct gaa att atc aaa ggg gag ctt tgg tcc aat ccc cta caa tac  1215
Ile Ala Glu Ile Ile Lys Gly Glu Leu Trp Ser Asn Pro Leu Gln Tyr
            365                 370                 375

tac ctg atg ggc gat ggg cca cgc aga gga gtt cga gtc cca cca agg  1263
Tyr Leu Met Gly Asp Gly Pro Arg Arg Gly Val Arg Val Pro Pro Arg
        380                 385                 390

cag cca gtg gag agt ccc agg tcc ttc agg ttc cag tct ggc          1305
Gln Pro Val Glu Ser Pro Arg Ser Phe Arg Phe Gln Ser Gly
    395                 400                 405

taagctctgc cctcgtgaga agctcttaca gaagagtcct taccaccttc tcagcttggc 1365

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aagtctccgg tagtttcaag gttgtggctt ccaagtcttt gctcttcttt ctcttggcca 1485

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tgccaagctc acgtgctgta gtttgtactg cttttctttg catggcttgg ttcctgtctg 1605

tgatcttcta ggtttttttgt tttcttttttt aaaagtggtt ctctatcaaa agaaagcttg 1665

acatatcctt accaagaact agccagattt catactgtgt tcccgatatc tatgtactgt 1725

gaagaactgt gagtttcgcc actgcaagat gggactgtat cccaatccag ccatcagccc 1785

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taccctgctt tttatctata gaatgagcag gtggctggta ggtgactact aggtaagagt 1905

gaagtattag gtgaggagtg ttttctgtca ccacattgtt cttgtaccaa tgcatcatga 1965

tcagcttgga tcagctactg actgtctgat atttctaacc cccaacacaa aaaaaaaaaa 2025

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<213> Rattus sp.

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Thr Ser Ala Leu Val Pro Glu Asp Leu Asp Leu Lys Gln Asp Gln Pro
20 25 30

Leu Ser Glu Glu Thr Asp Thr Val Arg Glu Met Glu Ala Ala Gly Glu
35 40 45

Ala Gly Ala Glu Gly Gly Ala Ser Pro Asp Ser Glu His Cys Asp Pro
50 55 60

Gln Leu Cys Leu Arg Val Ala Glu Asn Gly Cys Ala Ala Ala Ala Gly
65 70 75 80

Glu Gly Leu Glu Asp Gly Leu Ser Ser Ser Lys Cys Gly Asp Ala Pro
85 90 95

Leu Ala Ser Val Ala Ala Asn Asp Ser Asn Lys Asn Gly Cys Gln Leu
100 105 110

Ala Gly Pro Leu Ser Pro Ala Lys Pro Lys Thr Leu Glu Ala Ser Gly
115 120 125

Ala Val Gly Leu Gly Ser Gln Met Met Pro Gly Pro Lys Lys Thr Lys
130 135 140

Val Met Thr Thr Lys Gly Ala Ile Ser Ala Thr Thr Gly Lys Glu Gly
145 150 155 160

Glu Ala Gly Ala Ala Met Gln Glu Lys Lys Gly Val Gln Lys Glu Lys
165 170 175

Lys Ala Ala Gly Gly Gly Lys Asp Glu Thr Arg Pro Arg Ala Pro Lys
180 185 190

Ile Asn Asn Cys Met Asp Ser Leu Glu Ala Ile Asp Gln Glu Leu Ser
195 200 205

Asn Val Asn Ala Gln Ala Asp Arg Ala Phe Leu Gln Leu Glu Arg Lys
210 215 220

Phe Gly Arg Met Arg Arg Leu His Met Gln Arg Arg Ser Phe Ile Ile
225 230 235 240

Gln Asn Ile Pro Gly Phe Trp Val Thr Ala Phe Arg Asn His Pro Gln
245 250 255

Leu Ser Pro Met Ile Ser Gly Gln Asp Glu Asp Met Met Arg Tyr Met
260 265 270

Ile Asn Leu Glu Val Glu Glu Leu Lys His Pro Arg Ala Gly Cys Lys
275 280 285

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Phe Lys Phe Ile Phe Gln Ser Asn Pro Tyr Phe Arg Asn Glu Gly Leu
    290                 295                 300

Val Lys Glu Tyr Glu Arg Arg Ser Ser Gly Arg Val Val Ser Leu Ser
305                 310                 315                 320

Thr Pro Ile Arg Trp His Arg Gly Gln Glu Pro Gln Ala His Ile His
                325                 330                 335

Arg Asn Arg Glu Gly Asn Thr Ile Pro Ser Phe Phe Asn Trp Phe Ser
            340                 345                 350

Asp His Ser Leu Leu Glu Phe Asp Arg Ile Ala Glu Ile Ile Lys Gly
        355                 360                 365

Glu Leu Trp Ser Asn Pro Leu Gln Tyr Tyr Leu Met Gly Asp Gly Pro
    370                 375                 380

Arg Arg Gly Val Arg Val Pro Pro Arg Gln Pro Val Glu Ser Pro Arg
385                 390                 395                 400

Ser Phe Arg Phe Gln Ser Gly
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<222> (88)..(1329)

<400> 54

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tctcccacta gtctgacttc ttccaaa atg agc ggc ctg gat ggg ggc aac aag 114
                                Met Ser Gly Leu Asp Gly Gly Asn Lys
                                  1               5

ctc cct ctc gcc caa acc ggc ggc ctg gct gct ccc gac cat gcc tca   162
Leu Pro Leu Ala Gln Thr Gly Gly Leu Ala Ala Pro Asp His Ala Ser
 10                  15                  20                  25

gga gat ccg gac cta gac cag tgc caa ggg ctc cgt gaa gaa acc gag   210
Gly Asp Pro Asp Leu Asp Gln Cys Gln Gly Leu Arg Glu Glu Thr Glu
                 30                  35                  40

gcg aca cag gtg atg gcg aac aca ggt ggg ggc agc ctg gag acc gtt   258
Ala Thr Gln Val Met Ala Asn Thr Gly Gly Gly Ser Leu Glu Thr Val
             45                  50                  55

gcg gag ggg ggt gca tcc cag gat cct gtc gac tgt ggc ccc gcg ctc   306
Ala Glu Gly Gly Ala Ser Gln Asp Pro Val Asp Cys Gly Pro Ala Leu
         60                  65                  70
```

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cgc gtc cca gtt gcc ggg agt cgc ggc ggt gca gcg acc aaa gcc ggg   354
Arg Val Pro Val Ala Gly Ser Arg Gly Gly Ala Ala Thr Lys Ala Gly
     75                  80                  85

cag gag gat gct cca cct tct acg aaa ggt ctg gaa gca gcc tct gcc   402
Gln Glu Asp Ala Pro Pro Ser Thr Lys Gly Leu Glu Ala Ala Ser Ala
 90                  95                 100                 105

gcc gag gct gct gac agc agc cag aaa aat ggc tgt cag ctt gga gag   450
Ala Glu Ala Ala Asp Ser Ser Gln Lys Asn Gly Cys Gln Leu Gly Glu
                110                 115                 120

ccc cgt ggc cct gct ggg cag aag gct cta gaa gcc tgt ggc gca ggg   498
Pro Arg Gly Pro Ala Gly Gln Lys Ala Leu Glu Ala Cys Gly Ala Gly
            125                 130                 135

ggc ttg ggg tct cag atg ata ccg ggg aag aag gcc aag gaa gtg acg   546
Gly Leu Gly Ser Gln Met Ile Pro Gly Lys Lys Ala Lys Glu Val Thr
        140                 145                 150

act aaa aaa cgc gcc atc tcg gca gca gtg gaa aag gag gga gaa gca   594
Thr Lys Lys Arg Ala Ile Ser Ala Ala Val Glu Lys Glu Gly Glu Ala
    155                 160                 165

ggg gcg gcg atg gag gaa aag aag gta gtg cag aag gaa aaa aag gtg   642
Gly Ala Ala Met Glu Glu Lys Lys Val Val Gln Lys Glu Lys Lys Val
170                 175                 180                 185

gca gga ggg gtg aaa gag gag aca cgg ccc agg gcc ccg aag atc aat   690
Ala Gly Gly Val Lys Glu Glu Thr Arg Pro Arg Ala Pro Lys Ile Asn
                190                 195                 200

aac tgc atg gac tca ctg gag gcc atc gat caa gag ttg tca aac gta   738
Asn Cys Met Asp Ser Leu Glu Ala Ile Asp Gln Glu Leu Ser Asn Val
            205                 210                 215


aat gcc cag gct gac agg gcc ttc ctt cag ctt gag cgc aag ttt ggc   786
Asn Ala Gln Ala Asp Arg Ala Phe Leu Gln Leu Glu Arg Lys Phe Gly
        220                 225                 230

cgc atg cga agg ctc cac atg cag cgc aga agt ttc att atc cag aat   834
Arg Met Arg Arg Leu His Met Gln Arg Arg Ser Phe Ile Ile Gln Asn
    235                 240                 245

atc cca ggt ttc tgg gtt act gcc ttt cga aac cac ccc cag ctg tca   882
Ile Pro Gly Phe Trp Val Thr Ala Phe Arg Asn His Pro Gln Leu Ser
250                 255                 260                 265

cct atg atc agt ggc caa gat gaa gac atg ctg agg tac atg atc aat   930
Pro Met Ile Ser Gly Gln Asp Glu Asp Met Leu Arg Tyr Met Ile Asn
                270                 275                 280

ttg gag gtg gag gag ctt aaa cac ccc aga gca ggc tgc aaa ttc aag   978
Leu Glu Val Glu Glu Leu Lys His Pro Arg Ala Gly Cys Lys Phe Lys
            285                 290                 295

ttc atc ttt cag ggc aac ccc tac ttc cga aat gag ggg ctt gtc aag   1026
Phe Ile Phe Gln Gly Asn Pro Tyr Phe Arg Asn Glu Gly Leu Val Lys
        300                 305                 310
```

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gaa tat gaa cgc aga tcc tct ggc cgg gtg gtg tct ctt tcc act cca   1074
Glu Tyr Glu Arg Arg Ser Ser Gly Arg Val Val Ser Leu Ser Thr Pro
    315                 320                 325

atc cgc tgg cac cga ggc caa gac ccc cag gct cat atc cac aga aac   1122
Ile Arg Trp His Arg Gly Gln Asp Pro Gln Ala His Ile His Arg Asn
330                 335                 340                 345

cgg gaa ggg aac act atc cct agt ttc ttc aac tgg ttt tca gac cac   1170
Arg Glu Gly Asn Thr Ile Pro Ser Phe Phe Asn Trp Phe Ser Asp His
                350                 355                 360

agc ctt cta gaa ttc gac aga att gca gag att atc aaa gga gaa ctg   1218
Ser Leu Leu Glu Phe Asp Arg Ile Ala Glu Ile Ile Lys Gly Glu Leu
            365                 370                 375

tgg ccc aat ccc cta caa tac tac ctg atg ggt gaa ggg ccc cgt aga   1266
Trp Pro Asn Pro Leu Gln Tyr Tyr Leu Met Gly Glu Gly Pro Arg Arg
        380                 385                 390

gga att cga ggc cca cca agg cag cca gtg gag agc gcc aga tcc ttc   1314
Gly Ile Arg Gly Pro Pro Arg Gln Pro Val Glu Ser Ala Arg Ser Phe
    395                 400                 405

agg ttc cag tct ggc taatctctgt cctgtgagaa gcttctgcac aagtttcctt   1369
Arg Phe Gln Ser Gly
410

accacctcct cttggaccta tgcttggcca acagcatgca gtcttccatc tgctttctct 1429

tcatactgtg gattatcttt tcctttggtt ctaaatcttc agtaatcggt tgcaagattg 1489

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taaaatccat ttccttttctc tgtttcagcc tatgacaaaa ttgatgttta caggcctgct 3709

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aaacaaaaaa aaaaaaaaa 4148

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Cys Gln Gly Leu Arg Glu Glu Thr Glu Ala Thr Gln Val Met Ala Asn
35 40 45

Thr Gly Gly Gly Ser Leu Glu Thr Val Ala Glu Gly Gly Ala Ser Gln
50 55 60

Asp Pro Val Asp Cys Gly Pro Ala Leu Arg Val Pro Val Ala Gly Ser
65 70 75 80

Arg Gly Gly Ala Ala Thr Lys Ala Gly Gln Glu Asp Ala Pro Pro Ser
85 90 95

Thr Lys Gly Leu Glu Ala Ala Ser Ala Ala Glu Ala Ala Asp Ser Ser
100 105 110

Gln Lys Asn Gly Cys Gln Leu Gly Glu Pro Arg Gly Pro Ala Gly Gln
115 120 125

Lys Ala Leu Glu Ala Cys Gly Ala Gly Gly Leu Gly Ser Gln Met Ile
130 135 140

Pro Gly Lys Lys Ala Lys Glu Val Thr Thr Lys Lys Arg Ala Ile Ser
145 150 155 160

Ala Ala Val Glu Lys Glu Gly Glu Ala Gly Ala Ala Met Glu Glu Lys
165 170 175

Lys Val Val Gln Lys Glu Lys Lys Val Ala Gly Gly Val Lys Glu Glu
180 185 190

Thr Arg Pro Arg Ala Pro Lys Ile Asn Asn Cys Met Asp Ser Leu Glu
195 200 205

Ala Ile Asp Gln Glu Leu Ser Asn Val Asn Ala Gln Ala Asp Arg Ala
210 215 220

Phe Leu Gln Leu Glu Arg Lys Phe Gly Arg Met Arg Arg Leu His Met
225 230 235 240

Gln Arg Arg Ser Phe Ile Ile Gln Asn Ile Pro Gly Phe Trp Val Thr
245 250 255

Ala Phe Arg Asn His Pro Gln Leu Ser Pro Met Ile Ser Gly Gln Asp
260 265 270

Glu Asp Met Leu Arg Tyr Met Ile Asn Leu Glu Val Glu Glu Leu Lys
275 280 285

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His Pro Arg Ala Gly Cys Lys Phe Lys Phe Ile Phe Gln Gly Asn Pro
    290                 295                 300

Tyr Phe Arg Asn Glu Gly Leu Val Lys Glu Tyr Glu Arg Arg Ser Ser
305                 310                 315                 320

Gly Arg Val Val Ser Leu Ser Thr Pro Ile Arg Trp His Arg Gly Gln
                325                 330                 335

Asp Pro Gln Ala His Ile His Arg Asn Arg Glu Gly Asn Thr Ile Pro
            340                 345                 350

Ser Phe Phe Asn Trp Phe Ser Asp His Ser Leu Leu Glu Phe Asp Arg
        355                 360                 365

Ile Ala Glu Ile Ile Lys Gly Glu Leu Trp Pro Asn Pro Leu Gln Tyr
    370                 375                 380

Tyr Leu Met Gly Glu Gly Pro Arg Arg Gly Ile Arg Gly Pro Pro Arg
385                 390                 395                 400

Gln Pro Val Glu Ser Ala Arg Ser Phe Arg Phe Gln Ser Gly
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<213> Rattus sp.

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<221> CDS
<222> (1)..(801)

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  1               5                  10                  15

aac cat ggc tca gct ctg cac atc gct gcc tcg aat ctg tgc ctg ggc   96
Asn His Gly Ser Ala Leu His Ile Ala Ala Ser Asn Leu Cys Leu Gly
            20                  25                  30

gcc gcc aaa tgt tta ctg gag cat ggt gcc aac cca gcg ctg agg aat   144
Ala Ala Lys Cys Leu Leu Glu His Gly Ala Asn Pro Ala Leu Arg Asn
        35                  40                  45

cga aaa gga cag gta cca gcg gaa gtg gtc cca gac ccc atg gac atg   192
Arg Lys Gly Gln Val Pro Ala Glu Val Val Pro Asp Pro Met Asp Met
    50                  55                  60

tcc ctt gac aag gca gag gca gcc ctg gtg gcc aag gaa ttg cgg acg   240
Ser Leu Asp Lys Ala Glu Ala Ala Leu Val Ala Lys Glu Leu Arg Thr
65                  70                  75                  80

ctg cta gaa gag gct gtg cca ctg tcc tgc acc ctt cct aaa gtc aca   288
Leu Leu Glu Glu Ala Val Pro Leu Ser Cys Thr Leu Pro Lys Val Thr
                85                  90                  95
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cta ccc aac tat gac aac gtc cca ggc aat ctc atg ctc agc gcg ctg   336
Leu Pro Asn Tyr Asp Asn Val Pro Gly Asn Leu Met Leu Ser Ala Leu
            100                 105                 110

ggc ctg cgt cta gga gac cga gtg ctc ctc gat ggc cag aag acg ggc   384
Gly Leu Arg Leu Gly Asp Arg Val Leu Leu Asp Gly Gln Lys Thr Gly
        115                 120                 125

acg ctg agg ttc tgc ggg acc acc gag ttc gcc agt ggc cag tgg gtg   432
Thr Leu Arg Phe Cys Gly Thr Thr Glu Phe Ala Ser Gly Gln Trp Val
    130                 135                 140

ggc gtg gag cta gat gaa ccg gaa ggc aag aac gac ggc agc gtt ggg   480
Gly Val Glu Leu Asp Glu Pro Glu Gly Lys Asn Asp Gly Ser Val Gly
145                 150                 155                 160

ggt gtc cgg tac ttc atc tgc cct ccc aag cag ggt ctc ttt gca tct   528
Gly Val Arg Tyr Phe Ile Cys Pro Pro Lys Gln Gly Leu Phe Ala Ser
                165                 170                 175

gtg tcc aag gtc tcc aag gca gtg gat gca ccc ccc tca tct gtt acc   576
Val Ser Lys Val Ser Lys Ala Val Asp Ala Pro Pro Ser Ser Val Thr
            180                 185                 190

tcc acg ccc cgc act ccc cgg atg gac ttc tcc cgt gta acg ggc aaa   624
Ser Thr Pro Arg Thr Pro Arg Met Asp Phe Ser Arg Val Thr Gly Lys
        195                 200                 205

ggc cgg agg gaa cac aaa ggg aag aag aag tcc cca tct tcc cca tct   672
Gly Arg Arg Glu His Lys Gly Lys Lys Lys Ser Pro Ser Ser Pro Ser
    210                 215                 220

ctg ggc agc ctg cag cag cgt gaa ggg gcc aaa gct gaa gtt gga gac   720
Leu Gly Ser Leu Gln Gln Arg Glu Gly Ala Lys Ala Glu Val Gly Asp
225                 230                 235                 240

caa gtc ctt gtg gca ggc cag aac agg gat tgt gcg ttt cta tgg gaa   768
Gln Val Leu Val Ala Gly Gln Asn Arg Asp Cys Ala Phe Leu Trp Glu
                245                 250                 255

gac aga ctt tgc tcc agg tta ctg gta tgg cat tgaactggac cagcccacgg 821
Asp Arg Leu Cys Ser Arg Leu Leu Val Trp His
            260                 265

gcaagcatga cggctctgtg ttcggtgtcc ggtactttac ctgtgccccg aggcacgggg 881

tctttgcacc agcatctcgt atccagagga ttggtggatc cactgatccc cctggagaca 941

gtgttggagc aaaaaaagtg catcaagtga caatgacaca gcccaaacgc accttcacaa 1001

cagtccggac cccaaaggac attgcatcag agaactctat ctccaggtta ctcttctgct 1061

gctggtttcc ttggatgctg agggcggaga tgcagtctta gagacctgga tacctgacac 1121

agagacagag tcccctctag catctcctga cacaaggaga ccccagtcac cctaagatag 1181

agattcccag tgacacctcc agaatagaaa ccccgttagc cagccctcga ttactgaggt 1241

cccattatta acagatctcc catgacgact cccccaaata cagacctcat gttaccccaa 1301

aagagattcc ctgagtagca ccttcaggct agtccctgtc ccctacccct cagagcagat 1361
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ttcccccaat aaacattttc cacatcaccc aagggatgct gaccctctcc acgacaggac 1421

gttcttgagt taccagtgga ttagagtccc atgaatgaag acccccccca ccccggttct 1481

ccttaagcat aggtcatacc tccagaatag ccagccacat cactatcccc atgtaacatc 1541

agtctcctca aaatggcgtg aggtcactag aaagacctta tactctcctc tccttctcag 1601

agatgccctc cattcactta agtccctgtt ctcacccctg aacaagacac ctaattaacc 1661

ggcccactca cctcaattac aaacaccaaa atcgtcctgg aagcatgaat tacaggacag 1721

caagtcttcc tgccctctgc acccttgaga aacccccagt gccttgtatg aagcccaccc 1781

cacatggccc acagtccctg tgctggccaa ggctcccaga aaattctcta ttttttaaag 1841

taataacttc ccccccttg gggggatccc caaatttgga gaccccattc tagaacactg 1901

gggagttcaa attccagaga gaatatatat tatatataat ccccaattcc ccatgcttcc 1961

aagccctaca atctctagaa gaccccaaat ttctaattcc caggacttcc cctacccaag 2021

tcacagaatc ttcaaatccc cagggaatcc caaacttaag ataccaatcc caaaccctca 2081

ggaaatcccc caacacaagg tccttaggac cgggaggaag gaacctgttg ccaggagaac 2141

atcccaggct ctcagggcat ctcaaacctg actcccaggc accaggagac cccaaacaga 2201

aagtcccatc tttggaacaa ggataggact ctaataccct tagtccatgg atctttaatt 2261

tcccaacctc caaactccat gggccccacc ctcaagggaa cccccaagat ccaaatctct 2321

gataactaat atgtgcaggg ccccagggct ctaacaggac cccaaatcat ggagtcccta 2381

cttcaatcta ccttctggtc acaggtccaa gacactaaat ctgagtcatt ggccccaaag 2441

gacttcacag cacctgggcc agactaacag cctgagggag aacctgaggg ccccgtgggt 2501

ccagagcaga cctggggccc tgaccaccaa ggacagctca cgactgcccc ttcactgcat 2561

gtccctaaac tcagcatgac tcctgtcctc ttcaataaag acgtttctat ggcaaaaaaa 2621

aaaaaaaaaa aaaaaaaaaa aa 2643

<210> 57
<211> 267
<212> PRT
<213> Rattus sp.

<400> 57

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Leu Lys Gly Ala Arg Pro Arg Val Val Asn Ser Thr Cys Ser Asp Phe
  1               5                  10                  15

Asn His Gly Ser Ala Leu His Ile Ala Ala Ser Asn Leu Cys Leu Gly
             20                  25                  30

Ala Ala Lys Cys Leu Leu Glu His Gly Ala Asn Pro Ala Leu Arg Asn
         35                  40                  45
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Arg Lys Gly Gln Val Pro Ala Glu Val Val Pro Asp Pro Met Asp Met
50 55 60

Ser Leu Asp Lys Ala Glu Ala Ala Leu Val Ala Lys Glu Leu Arg Thr
65 70 75 80

Leu Leu Glu Glu Ala Val Pro Leu Ser Cys Thr Leu Pro Lys Val Thr
85 90 95

Leu Pro Asn Tyr Asp Asn Val Pro Gly Asn Leu Met Leu Ser Ala Leu
100 105 110

Gly Leu Arg Leu Gly Asp Arg Val Leu Leu Asp Gly Gln Lys Thr Gly
115 120 125

Thr Leu Arg Phe Cys Gly Thr Thr Glu Phe Ala Ser Gly Gln Trp Val
130 135 140

Gly Val Glu Leu Asp Glu Pro Glu Gly Lys Asn Asp Gly Ser Val Gly
145 150 155 160

Gly Val Arg Tyr Phe Ile Cys Pro Pro Lys Gln Gly Leu Phe Ala Ser
165 170 175

Val Ser Lys Val Ser Lys Ala Val Asp Ala Pro Pro Ser Ser Val Thr
180 185 190

Ser Thr Pro Arg Thr Pro Arg Met Asp Phe Ser Arg Val Thr Gly Lys
195 200 205

Gly Arg Arg Glu His Lys Gly Lys Lys Lys Ser Pro Ser Ser Pro Ser
210 215 220

Leu Gly Ser Leu Gln Gln Arg Glu Gly Ala Lys Ala Glu Val Gly Asp
225 230 235 240

Gln Val Leu Val Ala Gly Gln Asn Arg Asp Cys Ala Phe Leu Trp Glu
245 250 255

Asp Arg Leu Cys Ser Arg Leu Leu Val Trp His
260 265

<210> 58
<211> 2929
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (1)..(810)

<400> 58
gct gac tct acc tct aga tgg gct gag gcc ctc aga gaa atc tct ggt 48
Ala Asp Ser Thr Ser Arg Trp Ala Glu Ala Leu Arg Glu Ile Ser Gly
1 5 10 15

cgc tta gct gaa atg cct gca gat agt gga tac cct gca tac ctt ggt 96
Arg Leu Ala Glu Met Pro Ala Asp Ser Gly Tyr Pro Ala Tyr Leu Gly
20 25 30

```
gcc cga ctg gct tct ttc tat gag cga gca ggc aga gtg aaa tgt ctt   144
Ala Arg Leu Ala Ser Phe Tyr Glu Arg Ala Gly Arg Val Lys Cys Leu
         35                  40                  45

gga aac cct gag aga gaa ggg agt gtc agc att gta gga gca gtt tct   192
Gly Asn Pro Glu Arg Glu Gly Ser Val Ser Ile Val Gly Ala Val Ser
     50                  55                  60

cca cct ggt ggt gat ttt tct gat cca gtc aca tct gct act ctg ggt   240
Pro Pro Gly Gly Asp Phe Ser Asp Pro Val Thr Ser Ala Thr Leu Gly
 65                  70                  75                  80

att gtt cag gtg ttc tgg ggc ttg gat aag aag cta gct cag cgc aag   288
Ile Val Gln Val Phe Trp Gly Leu Asp Lys Lys Leu Ala Gln Arg Lys
                 85                  90                  95

cac ttc ccg tcc gtc aac tgg ctc att agc tac agc aag tac atg cgc   336
His Phe Pro Ser Val Asn Trp Leu Ile Ser Tyr Ser Lys Tyr Met Arg
            100                 105                 110

gcc ctg gac gag tac tat gac aaa cac ttc aca gag ttc gtg cct ctg   384
Ala Leu Asp Glu Tyr Tyr Asp Lys His Phe Thr Glu Phe Val Pro Leu
        115                 120                 125

agg acc aaa gct aag gag att ctg cag gaa gag gag gat ctg gcg gaa   432
Arg Thr Lys Ala Lys Glu Ile Leu Gln Glu Glu Glu Asp Leu Ala Glu
    130                 135                 140

atc gtg cag ctc gtg gga aag gcg tct tta gca gag aca gat aaa atc   480
Ile Val Gln Leu Val Gly Lys Ala Ser Leu Ala Glu Thr Asp Lys Ile
145                 150                 155                 160

acc ctg gag gta gca aaa ctt atc aaa gat gac ttc cta caa caa aat   528
Thr Leu Glu Val Ala Lys Leu Ile Lys Asp Asp Phe Leu Gln Gln Asn
                165                 170                 175

ggg tac act cct tat gac agg ttc tgt cca ttc tat aag acg gtg ggg   576
Gly Tyr Thr Pro Tyr Asp Arg Phe Cys Pro Phe Tyr Lys Thr Val Gly
            180                 185                 190

atg ctg tcc aac atg att tca ttc tat gat atg gcc cgc cgg gct gtg   624
Met Leu Ser Asn Met Ile Ser Phe Tyr Asp Met Ala Arg Arg Ala Val
        195                 200                 205

gag acc acc gcc cag agt gac aat aag atc aca tgg tcc att atc cgt   672
Glu Thr Thr Ala Gln Ser Asp Asn Lys Ile Thr Trp Ser Ile Ile Arg
    210                 215                 220

gag cac atg ggg gag att ctc tat aaa ctt tcc tcc atg aaa ttc aag   720
Glu His Met Gly Glu Ile Leu Tyr Lys Leu Ser Ser Met Lys Phe Lys
225                 230                 235                 240

gat cca gtg aag gat ggc gag gca aag atc aag gcc gac tac gca cag   768
Asp Pro Val Lys Asp Gly Glu Ala Lys Ile Lys Ala Asp Tyr Ala Gln
                245                 250                 255

ctt ctt gaa gat atg cag aac gca ttc cgt agc ctg gaa gat           810
Leu Leu Glu Asp Met Gln Asn Ala Phe Arg Ser Leu Glu Asp
            260                 265                 270
```

tagaactgtg acttctctcc tcctcttccg cagctcatat gtgtatattt tcctgaattt 870

ctcatctcca acccttgct tccatattgt gcagctttga gactagtgcc tcgtgcgttc 930

tcgttcattt tgctgtttct ttggtaggtc ttataaaaca cacattcctg tgctccgctg 990

tctgaaggag ctcctgacct ttgtctgaag tggtgaatgt agtgcatatg atacacagtg 1050

taacatacac attgtaacat atacgttctg taaacttgta tgtaaggtga ctacccctc 1110

cctcctctcc agtaaactgt aaacaggact actgcatgtg ctctattggg gatggaaggc 1170

cagatctcca taccgtggac aggtacataa ggaaactaga ccacttgcaa cttagtgttt 1230

gttgagtaac cattttgcag gaagtatttc catttaaaaa acaaaagatt aatgttccaa 1290

ttatttgtag cttccccagt atcaatcagg actgtttgtg gcgcacttgg gaactatttt 1350

gttttcctaa cagacgtttg caaggctgaa cgtaatagat aaatcagttc cctctgaaag 1410

tgtgaaagta aaaagagagc taggtggtca gacttaaatt gacatcgtct tgtttaagca 1470

tattttattt cactgagaga tttaatatca aggacttta tatactcaat tactaggaaa 1530

tctttttta agtacaattt aaaaatcatt gaaaatgtga tccacatcat agccattttc 1590

cttatattta gtcagatgag ctcagagtgg ggagggtgtg ggttagaata ccacaaggac 1650

acgcagcagt gcctgcaggc agtgtggccg ggggccagag cggcattgtt ttcacgaggt 1710

acgtgtgtgg cgtgtgtgtt tgcttgttga cactctgaaa acagcaagct taccagttcc 1770

aggaaatatt ttgttttctt tcactggctc agaaagctcc tcaaagtacc tggtccctga 1830

agcttcctat ctgttaatag agacgagaga ggttcttaaa tttaactggt gacaaaacaa 1890

aaagaaaaaa aagatcgatt tttgtcttgc tgttttggtg tgtttaaata ataattccat 1950

atttgcataa cgaggctcgc ttctgagagc ttggagatcg tgctccctct tcactctccg 2010

gggtgataat gctggcgcca tgctacctct tcaggagggg aaggggattg aacatggcta 2070

acactctcaa gtacacaagc gtaacgacaa agtatttatt ttaagccttg gtatgttgtt 2130

taaattatta ggtggtgcat ttcttatggt cttttgggta gacatagtat acacttcaga 2190

tgtaatgtgt aaatccttgc tagtgcatgt ctacacgata gactgctatt caagaaggat 2250

attcttccac ataacaattt aaaaactatt aaatcagata tggattatgc aatgacttgt 2310

tgagaggtgg attaacggtg ctgcttaatc agtttgcttc caatatggct tcgtatccag 2370

aagccctgac tagtggagat gagaaagatt tcaaaacctg tctgcctaca cctaccagca 2430

acctaggctt gtgatcagaa tgaatgatcc caagaaacta cttgaccaag tgtgttttgt 2490

tgtcctggat ttgagatgtg cgttcttcct ccctctgaga ctgttgatgt atgagtgtga 2550

agaagttaca gaaacaacgc tcagattttc acggtaactt tccctctgcc cacactgtag 2610

agtttcagat tgttcactga tagtgcttct ttcgtaagga tgtgttaaaa tatagcagtc 2670

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tttttaaaag attatgcagt tctctattta ttgtgctgtg cctggtccta agtgcagccg 2730

gttaaacaag tttcatatgt atttttccag tgttaaatct catacctatg ccctttggaa 2790

agctccatcc tgaacaatga atagaagagg ctatataaat tgcctcctta tcctaagat 2850

ttcactatct ttatgttaag agtaatgtat aattattaaa atctatgaaa aataaaaagt 2910

ggatttaaat taagagatc                                              2929
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<210> 59
<211> 270
<212> PRT
<213> Rattus sp.

<400> 59

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Ala Asp Ser Thr Ser Arg Trp Ala Glu Ala Leu Arg Glu Ile Ser Gly
  1               5                  10                  15

Arg Leu Ala Glu Met Pro Ala Asp Ser Gly Tyr Pro Ala Tyr Leu Gly
             20                  25                  30

Ala Arg Leu Ala Ser Phe Tyr Glu Arg Ala Gly Arg Val Lys Cys Leu
         35                  40                  45

Gly Asn Pro Glu Arg Glu Gly Ser Val Ser Ile Val Gly Ala Val Ser
     50                  55                  60

Pro Pro Gly Gly Asp Phe Ser Asp Pro Val Thr Ser Ala Thr Leu Gly
 65                  70                  75                  80

Ile Val Gln Val Phe Trp Gly Leu Asp Lys Lys Leu Ala Gln Arg Lys
                 85                  90                  95

His Phe Pro Ser Val Asn Trp Leu Ile Ser Tyr Ser Lys Tyr Met Arg
            100                 105                 110

Ala Leu Asp Glu Tyr Tyr Asp Lys His Phe Thr Glu Phe Val Pro Leu
        115                 120                 125

Arg Thr Lys Ala Lys Glu Ile Leu Gln Glu Glu Glu Asp Leu Ala Glu
    130                 135                 140

Ile Val Gln Leu Val Gly Lys Ala Ser Leu Ala Glu Thr Asp Lys Ile
145                 150                 155                 160

Thr Leu Glu Val Ala Lys Leu Ile Lys Asp Asp Phe Leu Gln Gln Asn
                165                 170                 175

Gly Tyr Thr Pro Tyr Asp Arg Phe Cys Pro Phe Tyr Lys Thr Val Gly
            180                 185                 190

Met Leu Ser Asn Met Ile Ser Phe Tyr Asp Met Ala Arg Arg Ala Val
        195                 200                 205

Glu Thr Thr Ala Gln Ser Asp Asn Lys Ile Thr Trp Ser Ile Ile Arg
    210                 215                 220
```

```
Glu His Met Gly Glu Ile Leu Tyr Lys Leu Ser Ser Met Lys Phe Lys
225                 230                 235                 240

Asp Pro Val Lys Asp Gly Glu Ala Lys Ile Lys Ala Asp Tyr Ala Gln
                245                 250                 255

Leu Leu Glu Asp Met Gln Asn Ala Phe Arg Ser Leu Glu Asp
            260                 265                 270


<210> 60
<211> 1489
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (1)..(1053)

<400> 60
gca cgg ctc ccg gcc ccg gag cat gcg cga cag cag ccc ctc ctc tcc   48
Ala Arg Leu Pro Ala Pro Glu His Ala Arg Gln Gln Pro Leu Leu Ser
  1               5                  10                  15

ggc cct gag ccc gga tcg tcc gcc cgg gtt cca gtt ccc ggc gtg gcc   96
Gly Pro Glu Pro Gly Ser Ser Ala Arg Val Pro Val Pro Gly Val Ala
             20                  25                  30

agt agg cgg cag ccg cga ggc ggc aag cca ccc agc ggg gac ggc ctg   144
Ser Arg Arg Gln Pro Arg Gly Gly Lys Pro Pro Ser Gly Asp Gly Leu
         35                  40                  45

gag tcg ggc ccc tct cca cgc ccc ctt ctc cac gcg cgc ggg gag gca   192
Glu Ser Gly Pro Ser Pro Arg Pro Leu Leu His Ala Arg Gly Glu Ala
     50                  55                  60

ggg ctc cac cgc cag tct gga agg gtt cca cat aca gga acg gcc tac   240
Gly Leu His Arg Gln Ser Gly Arg Val Pro His Thr Gly Thr Ala Tyr
 65                  70                  75                  80

ttc gca gat gag ccc acc gag gct cag gct ccg ggc gga ttc tgc gtg   288
Phe Ala Asp Glu Pro Thr Glu Ala Gln Ala Pro Gly Gly Phe Cys Val
                 85                  90                  95

tca ccc tcg ctc ctt ggg gtc cgc tgg ccg gcc tgt gcc acc cgg acg   336
Ser Pro Ser Leu Leu Gly Val Arg Trp Pro Ala Cys Ala Thr Arg Thr
            100                 105                 110

ccc ggc tca ctg cct ctg tct ccc cca tca gcg cag ccc cgg acg cta   384
Pro Gly Ser Leu Pro Leu Ser Pro Pro Ser Ala Gln Pro Arg Thr Leu
        115                 120                 125



tgg ccc acc cct cca gct ggc ccc tcg agt agg atg gta gca cgt aac   432
Trp Pro Thr Pro Pro Ala Gly Pro Ser Ser Arg Met Val Ala Arg Asn
    130                 135                 140

cag gtg gca gcc gac aat gcg atc tcc ccg gca tca gag ccc cga cgg   480
Gln Val Ala Ala Asp Asn Ala Ile Ser Pro Ala Ser Glu Pro Arg Arg
145                 150                 155                 160
```

```
cgg cca gag cca tcc tcg tcc tcg tct tcg tcc tcg ccg gcg gcc ccg   528
Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Ser Ser Pro Ala Ala Pro
                165                 170                 175

gcg cgt ccc cgg ccc tgc ccg gtg gtc ccg gcc ccg gct ccg ggc gac   576
Ala Arg Pro Arg Pro Cys Pro Val Val Pro Ala Pro Ala Pro Gly Asp
            180                 185                 190

act cac ttc cgc acc ttc cgc tcc cac tct gat tac cgg cgc atc acg   624
Thr His Phe Arg Thr Phe Arg Ser His Ser Asp Tyr Arg Arg Ile Thr
        195                 200                 205

cgg acc agc gct ctc ctg gac gcc tgc ggc ttc tac tgg gga ccc ctg   672
Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe Tyr Trp Gly Pro Leu
    210                 215                 220

agc gtg cat ggg gcg cac gaa cgg ctg cgt gcc gag ccc gtg ggc acc   720
Ser Val His Gly Ala His Glu Arg Leu Arg Ala Glu Pro Val Gly Thr
225                 230                 235                 240

ttc ttg gtg cgc gac agt cgc cag cgg aac tgc ttc ttc gcg ctc agc   768
Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys Phe Phe Ala Leu Ser
                245                 250                 255

gtg aag atg gct tcg ggc ccc acg agc att cgt gtg cac ttc cag gcc   816
Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg Val His Phe Gln Ala
            260                 265                 270

ggc cgc ttc cac ctg gac ggc agc cgc gag acc ttc gac tgc ctc ttc   864
Gly Arg Phe His Leu Asp Gly Ser Arg Glu Thr Phe Asp Cys Leu Phe
        275                 280                 285

gag ctg ctg gag cac tac gtg gcg gcg ccg cgc cgc atg ttg ggg gcc   912
Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg Arg Met Leu Gly Ala
    290                 295                 300

cca ctg cgc cag cgc cgc gtg cgg ccg ctg cag gag ctg tgt cgc cag   960
Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln Glu Leu Cys Arg Gln
305                 310                 315                 320

cgc atc gtg gcc gcc gtg ggt cgc gag aac ctg gca cgc atc cct ctt   1008
Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu Ala Arg Ile Pro Leu
                325                 330                 335

aac ccg gta ctc cgt gac tac ctg agt tcc ttc ccc ttc cag atc       1053
Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe Pro Phe Gln Ile
            340                 345                 350

tgaccggctg ccgccgtgcc cgcagcatta agtgggagcg ccttattatt tcttattatt 1113

aattattatt atttttctgg aaccacgtgg gagccctccc cgcctaggtc ggagggagtg 1173

ggtgtggagg gtgagatgcc tcccacttct ggctggagac cttatcccgc ctctcggggg 1233

gcctcccctc ctggtgctcc ctcccggtcc ccctggttgt agcagcttgt gtctggggcc 1293

aggacctgaa ctccacgcct acctctccat gtttacatgt tcccagtatc tttgcacaaa 1353

ccaggggtgg gggagggtct ctggcttcat ttttctgctg tgcagaatat tctatttttat 1413
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atttttacat ccagtttaga taataaactt tattatgaaa gttttttttt taaagaaaaa 1473

aaaaaaaaaa aaaaaa 1489

<210> 61
<211> 351
<212> PRT
<213> Rattus sp.

<400> 61

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Ala Arg Leu Pro Ala Pro Glu His Ala Arg Gln Gln Pro Leu Leu Ser
  1               5                  10                  15

Gly Pro Glu Pro Gly Ser Ser Ala Arg Val Pro Val Pro Gly Val Ala
            20                  25                  30

Ser Arg Arg Gln Pro Arg Gly Gly Lys Pro Pro Ser Gly Asp Gly Leu
        35                  40                  45

Glu Ser Gly Pro Ser Pro Arg Pro Leu Leu His Ala Arg Gly Glu Ala
    50                  55                  60

Gly Leu His Arg Gln Ser Gly Arg Val Pro His Thr Gly Thr Ala Tyr
65                  70                  75                  80

Phe Ala Asp Glu Pro Thr Glu Ala Gln Ala Pro Gly Gly Phe Cys Val
                85                  90                  95

Ser Pro Ser Leu Leu Gly Val Arg Trp Pro Ala Cys Ala Thr Arg Thr
            100                 105                 110

Pro Gly Ser Leu Pro Leu Ser Pro Pro Ser Ala Gln Pro Arg Thr Leu
        115                 120                 125

Trp Pro Thr Pro Pro Ala Gly Pro Ser Ser Arg Met Val Ala Arg Asn
    130                 135                 140

Gln Val Ala Ala Asp Asn Ala Ile Ser Pro Ala Ser Glu Pro Arg Arg
145                 150                 155                 160

Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Ser Ser Pro Ala Ala Pro
                165                 170                 175

Ala Arg Pro Arg Pro Cys Pro Val Val Pro Ala Pro Ala Pro Gly Asp
            180                 185                 190

Thr His Phe Arg Thr Phe Arg Ser His Ser Asp Tyr Arg Arg Ile Thr
        195                 200                 205

Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe Tyr Trp Gly Pro Leu
    210                 215                 220

Ser Val His Gly Ala His Glu Arg Leu Arg Ala Glu Pro Val Gly Thr
225                 230                 235                 240

Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys Phe Phe Ala Leu Ser
                245                 250                 255

Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg Val His Phe Gln Ala
            260                 265                 270
```

```
Gly Arg Phe His Leu Asp Gly Ser Arg Glu Thr Phe Asp Cys Leu Phe
        275                 280                 285

Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg Arg Met Leu Gly Ala
    290                 295                 300

Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln Glu Leu Cys Arg Gln
305                 310                 315                 320

Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu Ala Arg Ile Pro Leu
                325                 330                 335

Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe Pro Phe Gln Ile
            340                 345                 350


<210> 62
<211> 1194
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (130)..(765)

<400> 62
ggcacggctc ccggccccgg agcatgcgcg acagcagccc cggaaccccc agccgcggcg 60

ccccgcgtcc cgccgccagc gcagccccgg acgctatggc ccacccctcc agctggcccc 120

tcgagtagg atg gta gca cgt aac cag gtg gca gcc gac aat gcg atc tcc 171
          Met Val Ala Arg Asn Gln Val Ala Ala Asp Asn Ala Ile Ser
            1               5                  10

ccg gca tca gag ccc cga cgg cgg cca gag cca tcc tcg tcc tcg tct   219
Pro Ala Ser Glu Pro Arg Arg Arg Pro Glu Pro Ser Ser Ser Ser Ser
 15                  20                  25                  30

tcg tcc tcg ccg gcg gcc ccg gcg cgt ccc cgg ccc tgc ccg gtg gtc   267
Ser Ser Ser Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Val Val
                35                  40                  45

ccg gcc ccg gct ccg ggc gac act cac ttc cgc acc ttc cgc tcc cac   315
Pro Ala Pro Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His
            50                  55                  60

tct gat tac cgg cgc atc acg cgg acc agc gct ctc ctg gac gcc tgc   363
Ser Asp Tyr Arg Arg Ile Thr Arg Thr Ser Ala Leu Leu Asp Ala Cys
        65                  70                  75

ggc ttc tac tgg gga ccc ctg agc gtg cat ggg gcg cac gaa cgg ctg   411
Gly Phe Tyr Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu
    80                  85                  90

cgt gcc gag ccc gtg ggc acc ttc ttg gtg cgc gac agt cgc cag cgg   459
Arg Ala Glu Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg
 95                 100                 105                 110
```

```
aac tgc ttc ttc gcg ctc agc gtg aag atg gct tcg ggc ccc acg agc   507
Asn Cys Phe Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser
                115                 120                 125

att cgt gtg cac ttc cag gcc ggc cgc ttc cac ctg gac ggc agc cgc   555
Ile Arg Val His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg
            130                 135                 140

gag acc ttc gac tgc ctc ttc gag ctg ctg gag cac tac gtg gcg gcg   603
Glu Thr Phe Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala
        145                 150                 155

ccg cgc cgc atg ttg ggg gcc cca ctg cgc cag cgc cgc gtg cgg ccg   651
Pro Arg Arg Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro
    160                 165                 170

ctg cag gag ctg tgt cgc cag cgc atc gtg gcc gcc gtg ggt cgc gag   699
Leu Gln Glu Leu Cys Arg Gln Arg Ile Val Ala Ala Val Gly Arg Glu
175                 180                 185                 190

aac ctg gca cgc atc cct ctt aac ccg gta ctc cgt gac tac ctg agt   747
Asn Leu Ala Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser
                195                 200                 205

tcc ttc ccc ttc cag atc tgaccggctg ccgccgtgcc cgcagcatta          795
Ser Phe Pro Phe Gln Ile
            210

agtgggagcg ccttattatt tcttattatt aattattatt atttttctgg aaccacgtgg 855

gagccctccc cgcctaggtc ggagggagtg ggtgtggagg gtgagatgcc tcccacttct 915

ggctggagac cttatcccgc ctctcggggg gcctcccctc ctggtgctcc ctcccggtcc 975

ccctggttgt agcagcttgt gtctggggcc aggacctgaa ctccacgcct acctctccat 1035

gtttacatgt tcccagtatc tttgcacaaa ccaggggtgg gggagggtct ctggcttcat 1095

ttttctgctg tgcagaatat tctatttttat atttttacat ccagtttaga taataaactt 1155

tattatgaaa gttttttttt taaaaaaaaa aaaaaaaaa                         1194
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<210> 63
<211> 212
<212> PRT
<213> Rattus sp.

<400> 63

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Met Val Ala Arg Asn Gln Val Ala Ala Asp Asn Ala Ile Ser Pro Ala
  1               5                  10                  15

Ser Glu Pro Arg Arg Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Ser
             20                  25                  30

Ser Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Val Val Pro Ala
         35                  40                  45

Pro Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His Ser Asp
     50                  55                  60
```

```
Tyr Arg Arg Ile Thr Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe
 65                  70                  75                  80

Tyr Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu Arg Ala
                 85                  90                  95

Glu Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys
            100                 105                 110

Phe Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg
        115                 120                 125

Val His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg Glu Thr
    130                 135                 140

Phe Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg
145                 150                 155                 160

Arg Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln
                165                 170                 175

Glu Leu Cys Arg Gln Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu
            180                 185                 190

Ala Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe
        195                 200                 205

Pro Phe Gln Ile
    210
```



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<210> 64
<211> 600
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (52)..(336)

<400> 64
cttccaaaga ctgcagcgcc tcagggccca ggtttcaaca gattcttcaa a atg cca  57
                                                          Met Pro
                                                            1

tcc caa atg gag cat gcc atg gaa acc atg atg ctt aca ttt cac agg   105
Ser Gln Met Glu His Ala Met Glu Thr Met Met Leu Thr Phe His Arg
          5                  10                  15

ttt gca ggg gaa aaa aac tac ttg aca aag gag gac ctg aga gtg ctc   153
Phe Ala Gly Glu Lys Asn Tyr Leu Thr Lys Glu Asp Leu Arg Val Leu
     20                  25                  30

atg gaa agg gag ttc cct ggg ttt ttg gaa aat caa aag gac cct ctg   201
Met Glu Arg Glu Phe Pro Gly Phe Leu Glu Asn Gln Lys Asp Pro Leu
 35                  40                  45                  50
```

```
gct gtg gac aaa ata atg aaa gac ctg gac cag tgc cga gat gga aaa   249
Ala Val Asp Lys Ile Met Lys Asp Leu Asp Gln Cys Arg Asp Gly Lys
                55                  60                  65

gtg ggc ttc cag agc ttt cta tca cta gtg gcg ggg ctc atc att gca   297
Val Gly Phe Gln Ser Phe Leu Ser Leu Val Ala Gly Leu Ile Ile Ala
            70                  75                  80

tgc aat gac tat ttt gta gta cac atg aag cag aag aag taggccaact    346
Cys Asn Asp Tyr Phe Val Val His Met Lys Gln Lys Lys
        85                  90                  95

ggagccctgg tacccacacc ttgatgcgtc ctctcccatg gggtcaactg aggaatctgc 406

cccactgctt cctgtgagca gatcaggacc cttaggaaat gtgcaaataa catccaactc 466

caattcgaca agcagagaaa gaaaagttaa tccaatgaca gaggagcttt cgagttttat 526

attgtttgca tccggttgcc ctcaataaag aaagtctttt tttttaagtt ccgaaaaaaa 586

aaaaaaaaaa aaaa                                                  600


<210> 65
<211> 95
<212> PRT
<213> Rattus sp.

<400> 65
Met Pro Ser Gln Met Glu His Ala Met Glu Thr Met Met Leu Thr Phe
  1               5                  10                  15

His Arg Phe Ala Gly Glu Lys Asn Tyr Leu Thr Lys Glu Asp Leu Arg
            20                  25                  30

Val Leu Met Glu Arg Glu Phe Pro Gly Phe Leu Glu Asn Gln Lys Asp
        35                  40                  45

Pro Leu Ala Val Asp Lys Ile Met Lys Asp Leu Asp Gln Cys Arg Asp
    50                  55                  60

Gly Lys Val Gly Phe Gln Ser Phe Leu Ser Leu Val Ala Gly Leu Ile
65                  70                  75                  80

Ile Ala Cys Asn Asp Tyr Phe Val Val His Met Lys Gln Lys Lys
                85                  90                  95


<210> 66
<211> 639
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (1)..(636)

<400> 66
atg gcg tac gcc tat ctc ttc aag tac atc atc atc ggc gac aca ggt   48
Met Ala Tyr Ala Tyr Leu Phe Lys Tyr Ile Ile Ile Gly Asp Thr Gly
```

```
  1               5                  10                  15

gtt ggt aaa tcg tgc tta ttg cta cag ttt aca gac aag agg ttt cag   96
Val Gly Lys Ser Cys Leu Leu Leu Gln Phe Thr Asp Lys Arg Phe Gln
            20                  25                  30

ccg gtg cat gac ctc aca att ggt gta gag ttt ggt gct cga atg ata   144
Pro Val His Asp Leu Thr Ile Gly Val Glu Phe Gly Ala Arg Met Ile
        35                  40                  45

acc att gat ggg aaa cag ata aaa ctc cag atc tgg gat aca gca ggg   192
Thr Ile Asp Gly Lys Gln Ile Lys Leu Gln Ile Trp Asp Thr Ala Gly
    50                  55                  60

cag gag tcc ttt cgt tct atc aca agg tca tat tac aga ggt gca gcg   240
Gln Glu Ser Phe Arg Ser Ile Thr Arg Ser Tyr Tyr Arg Gly Ala Ala
65                  70                  75                  80

ggg gct tta cta gtg tat gat att aca agg aga gac acg ttc aac cac   288
Gly Ala Leu Leu Val Tyr Asp Ile Thr Arg Arg Asp Thr Phe Asn His
                85                  90                  95

ttg aca acc tgg tta gaa gac gcc cgt cag cat tcc aat tcc aac atg   336
Leu Thr Thr Trp Leu Glu Asp Ala Arg Gln His Ser Asn Ser Asn Met
            100                 105                 110



gtc atc atg ctt att gga aat aaa agt gac tta gaa tct agg aga gaa   384
Val Ile Met Leu Ile Gly Asn Lys Ser Asp Leu Glu Ser Arg Arg Glu
        115                 120                 125

gtg aaa aag gaa gaa ggt gaa gct ttt gca cga gag cat gga ctt atc   432
Val Lys Lys Glu Glu Gly Glu Ala Phe Ala Arg Glu His Gly Leu Ile
    130                 135                 140

ttc atg gaa act tct gcc aag act gct tct aat gta gag gag gca ttt   480
Phe Met Glu Thr Ser Ala Lys Thr Ala Ser Asn Val Glu Glu Ala Phe
145                 150                 155                 160

att aac aca gca aaa gaa att tat gaa aaa atc caa gaa ggg gtc ttt   528
Ile Asn Thr Ala Lys Glu Ile Tyr Glu Lys Ile Gln Glu Gly Val Phe
                165                 170                 175

gac att aat aat gag gca aac ggc atc aaa att ggc cct cag cat gct   576
Asp Ile Asn Asn Glu Ala Asn Gly Ile Lys Ile Gly Pro Gln His Ala
            180                 185                 190

gct acc aat gca tct cac gga ggc aac caa gga ggg cag cag gca ggg   624
Ala Thr Asn Ala Ser His Gly Gly Asn Gln Gly Gly Gln Gln Ala Gly
        195                 200                 205

gga ggc tgc tgc tga                                              639
Gly Gly Cys Cys
    210
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<210> 67
<211> 212
<212> PRT
<213> Rattus sp.

<400> 67
Met Ala Tyr Ala Tyr Leu Phe Lys Tyr Ile Ile Ile Gly Asp Thr Gly
1 5 10 15

Val Gly Lys Ser Cys Leu Leu Leu Gln Phe Thr Asp Lys Arg Phe Gln
20 25 30

Pro Val His Asp Leu Thr Ile Gly Val Glu Phe Gly Ala Arg Met Ile
35 40 45

Thr Ile Asp Gly Lys Gln Ile Lys Leu Gln Ile Trp Asp Thr Ala Gly
50 55 60

Gln Glu Ser Phe Arg Ser Ile Thr Arg Ser Tyr Tyr Arg Gly Ala Ala
65 70 75 80

Gly Ala Leu Leu Val Tyr Asp Ile Thr Arg Arg Asp Thr Phe Asn His
85 90 95

Leu Thr Thr Trp Leu Glu Asp Ala Arg Gln His Ser Asn Ser Asn Met
100 105 110

Val Ile Met Leu Ile Gly Asn Lys Ser Asp Leu Glu Ser Arg Arg Glu
115 120 125

Val Lys Lys Glu Glu Gly Glu Ala Phe Ala Arg Glu His Gly Leu Ile
130 135 140

Phe Met Glu Thr Ser Ala Lys Thr Ala Ser Asn Val Glu Glu Ala Phe
145 150 155 160

Ile Asn Thr Ala Lys Glu Ile Tyr Glu Lys Ile Gln Glu Gly Val Phe
165 170 175

Asp Ile Asn Asn Glu Ala Asn Gly Ile Lys Ile Gly Pro Gln His Ala
180 185 190

Ala Thr Asn Ala Ser His Gly Gly Asn Gln Gly Gly Gln Gln Ala Gly
195 200 205

Gly Gly Cys Cys
210

<210> 68
<211> 816
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (1)..(813)

<400> 68
atg gtg ctg ctc aag gaa tat cgg gtc atc ctg cct gtg tct gta gat 48
Met Val Leu Leu Lys Glu Tyr Arg Val Ile Leu Pro Val Ser Val Asp
1 5 10 15

```
gag tat caa gtg ggg cag ctg tac tct gtg gct gaa gcc agt aaa aat     96
Glu Tyr Gln Val Gly Gln Leu Tyr Ser Val Ala Glu Ala Ser Lys Asn
         20                  25                  30

gaa act ggt ggt ggg gaa ggt gtg gag gtc ctg gtg aac gag ccc tac    144
Glu Thr Gly Gly Gly Glu Gly Val Glu Val Leu Val Asn Glu Pro Tyr
     35                  40                  45

gag aag gat gat ggc gag aaa ggc cag tac aca cac aag atc tac cac    192
Glu Lys Asp Asp Gly Glu Lys Gly Gln Tyr Thr His Lys Ile Tyr His
 50                  55                  60

tta cag agc aaa gtt ccc acg ttt gtt cga atg ctg gcc cca gaa ggc    240
Leu Gln Ser Lys Val Pro Thr Phe Val Arg Met Leu Ala Pro Glu Gly
 65                  70                  75                  80

gcc ctg aat ata cat gag aaa gcc tgg aat gcc tac cct tac tgc aga    288
Ala Leu Asn Ile His Glu Lys Ala Trp Asn Ala Tyr Pro Tyr Cys Arg
             85                  90                  95

acc gtt att aca aat gag tac atg aag gaa gac ttt ctc att aaa att    336
Thr Val Ile Thr Asn Glu Tyr Met Lys Glu Asp Phe Leu Ile Lys Ile
        100                 105                 110

gaa acc tgg cac aag cca gac ctt ggc acc cag gag aat gtg cat aaa    384
Glu Thr Trp His Lys Pro Asp Leu Gly Thr Gln Glu Asn Val His Lys
    115                 120                 125

ctg gag cct gag gca tgg aaa cat gtg gaa gct ata tat ata gac atc    432
Leu Glu Pro Glu Ala Trp Lys His Val Glu Ala Ile Tyr Ile Asp Ile
130                 135                 140

gct gat cga agc caa gta ctt agc aag gat tac aag gca gag gaa gac    480
Ala Asp Arg Ser Gln Val Leu Ser Lys Asp Tyr Lys Ala Glu Glu Asp
145                 150                 155                 160

cca gca aaa ttt aaa tct atc aaa aca gga cga gga cca ttg ggc ccg    528
Pro Ala Lys Phe Lys Ser Ile Lys Thr Gly Arg Gly Pro Leu Gly Pro
            165                 170                 175

aat tgg aag caa gaa ctt gtc aat cag aag gac tgc cca tat atg tgt    576
Asn Trp Lys Gln Glu Leu Val Asn Gln Lys Asp Cys Pro Tyr Met Cys
        180                 185                 190

gca tac aaa ctg gtt act gtc aag ttc aag tgg tgg ggc ttg cag aac    624
Ala Tyr Lys Leu Val Thr Val Lys Phe Lys Trp Trp Gly Leu Gln Asn
    195                 200                 205

aaa gtg gaa aac ttt ata cat aag caa gag aag cgt ctg ttt aca aac    672
Lys Val Glu Asn Phe Ile His Lys Gln Glu Lys Arg Leu Phe Thr Asn
    210                 215                 220

ttt cac agg cag ctg ttc tgt tgg ctt gat aaa tgg gtt gat ctg act    720
Phe His Arg Gln Leu Phe Cys Trp Leu Asp Lys Trp Val Asp Leu Thr
225                 230                 235                 240

atg gat gac att cgg agg atg gaa gaa gag acg aag aga cag ctg gat    768
Met Asp Asp Ile Arg Arg Met Glu Glu Glu Thr Lys Arg Gln Leu Asp
            245                 250                 255
```

gag atg aga caa aag gac ccc gtg aaa gga atg aca gca gat gac tag 816
Glu Met Arg Gln Lys Asp Pro Val Lys Gly Met Thr Ala Asp Asp
260 265 270

<210> 69
<211> 2263
<212> DNA
<213> Simian sp.

<400> 69
cgctctcctc ctccccttc tctagcagta gccttcttaa tgtagtttaa tggctttaca 60

aagaaagcca ggcagaggag cacttctcag tggctgtggt cggaccatga cctagctgac 120

catgaacttg gaagggcttg aaatgatagc agttctgatc gtcattgtgc tttttgttaa 180

attattggaa cagtttgggc tgattgaagc aggtttagaa gacagcgtgg aagatgaact 240

ggagatggcc actgtcaggc atcggcctga ggcccttgag cttctggaag cccagagcaa 300

atttaccaag aaagagcttc agatccttta cagaggattt aagaacgaat gccccagtgg 360

tgttgttaat gaagaaacct tcaaagagat ttactcgcag ttctttccac agggagactc 420

tacaacatat gcacattttc tgttcaatgc gtttgatacg gaccacaatg gagctgtgag 480

tttcgaggat ttcatcaaag gtctttccat tttgctccgg gggacagtac aagaaaaact 540

caattgggca tttaatctgt atgatataaa taaagatggc tacatcacta aagaggaaat 600

gcttgatata atgaaagcaa tatacgacat gatgggtaaa tgtacatatc ctgtcctcaa 660

agaagatgca cccagacaac acgtcgaaac atttttcag aaaatggaca aaaataaaga 720

tggggttgtt accatagatg agttcattga aagctgccaa aaagatgaaa acataatgcg 780

ctccatgcag ctctttgaaa atgtgattta acttgtcaac tagatcctga atccaacaga 840

caaatgtgaa ctattctacc acccttaaag tcggagctac cacttttagc atagattgct 900

cagcttgaca ctgaagcata ttatgcaaac aagctttgtt ttaatataaa gcaatcccca 960

aaagatttga gtttctcagt tataaatttg catcctttcc ataatgccac tgagttcatg 1020

ggatgttcta actcatttca tactctgtga atattcaaaa gtaatagaat ctggcatata 1080

gttttattga ttccttagcc atgggattat tgaggctttc acatatcagt gattttaaaa 1140

taccagtgtt ttttgctact catttgtatg tattcagtcc taggattttg aatggttttc 1200

taatatactg acatctgcat ttaatttcca gaaattaaat taattttcat gtctgaatgc 1260

tgtaattcca tttatatact ttaagtaaac aaataagatt actacaatta aacacatagt 1320

tccagtttct atggccttca cttcccacct tctattagaa attaatttta tctggtattt 1380

ttaaacattt aaaaatttat catcagatat cagcatatgc ctaattatgc ctaatgaaac 1440

ttaataagca tttaattttc catcatacat tatagtcaag gcctatatac tatatataat 1500

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tttggatttg tttaatctta caggctgttt tccattgtat catcaagtgg aagttcaaga 1560

cggcatcaaa caaaacaagg atgtttacag acatatgcaa agggtcagga tatctatcct 1620

ccagtatatg ttaatgctta ataacaagta atcctaacag cattaaaggc caaatctgtc 1680

ctctttcccc tgacttcctt acagcatgtt tatattacaa gccattcagg gacaaagaaa 1740

ccttgactac cccactgtct actaggaaca aacaaacagc aagcaaaatt cactttgaaa 1800

gcaccagtgg ttccattaca ttgacaacta ctaccaagat tcagtagaaa ataagtgctc 1860

aacaactaat ccagattaca atatgattta gtgcatcata aaattccaac aattcagatt 1920

atttttaatc acctcagcca caactgtaaa gttgccacat tactaaagac acacacatcg 1980

tccctgtttt gtagaaatat cacaaagacc aagaggctac agaaggagga aatttgcaac 2040

tgtctttgca acaataaatc aggtatctat tctggtgtag agataggatg ttgaaagctg 2100

ccctgctatc accagtgtag aaattaagag tagtacaata catgtacact gaaatttgcc 2160

atcgcgtgtt tgtgtaaact caatgtgcac attttgtatt tcaaaaagaa aaaataaaag 2220

caaaataaaa tgtttataac tctaaaaaaa aaaaaaaaaa aaa                   2263


<210> 70
<211> 229
<212> PRT
<213> Simian sp.

<400> 70
Met Asn Leu Glu Gly Leu Glu Met Ile Ala Val Leu Ile Val Ile Val
  1               5                  10                  15

Leu Phe Val Lys Leu Leu Glu Gln Phe Gly Leu Ile Glu Ala Gly Leu
            20                  25                  30

Glu Asp Ser Val Glu Asp Glu Leu Glu Met Ala Thr Val Arg His Arg
        35                  40                  45

Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys Phe Thr Lys Lys
    50                  55                  60

Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly
65                  70                  75                  80

Val Val Asn Glu Glu Thr Phe Lys Glu Ile Tyr Ser Gln Phe Phe Pro
                85                  90                  95

Gln Gly Asp Ser Thr Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp
            100                 105                 110

Thr Asp His Asn Gly Ala Val Ser Phe Glu Asp Phe Ile Lys Gly Leu
        115                 120                 125

Ser Ile Leu Leu Arg Gly Thr Val Gln Glu Lys Leu Asn Trp Ala Phe
    130                 135                 140
```

```
Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Thr Lys Glu Glu Met
145                 150                 155                 160

Leu Asp Ile Met Lys Ala Ile Tyr Asp Met Met Gly Lys Cys Thr Tyr
                165                 170                 175

Pro Val Leu Lys Glu Asp Ala Pro Arg Gln His Val Glu Thr Phe Phe
            180                 185                 190

Gln Lys Met Asp Lys Asn Lys Asp Gly Val Val Thr Ile Asp Glu Phe
        195                 200                 205

Ile Glu Ser Cys Gln Lys Asp Glu Asn Ile Met Arg Ser Met Gln Leu
    210                 215                 220

Phe Glu Asn Val Ile
225
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<210> 71
<211> 2259
<212> DNA
<213> Simian sp.

<400> 71
gtcgacagac gcccctggcc ggtggactcc tgagtcttac tcctgcaccc tgcgtcccca 60

gacatgaatg tgaggagagt ggaaagcatt tcggctcagc tggaggaggc cagctccaca 120

ggcggtttcc tgtatgctca gaacagcacc aagcgcagca ttaaagagcg gctcatgaag 180

ctcttgccct gctcagctgc caaaacatcg tctcctgcta ttcaaaacag cgtggaagat 240

gaactggaga tggccactgt caggcatcgg cctgaggccc ttgagcttct ggaagcccag 300

agcaaattta ccaagaaaga gcttcagatc ctttacagag gatttaagaa cgaatgcccc 360

agtggtgttg ttaatgaaga aaccttcaaa gagatttact cgcagttctt tccacaggga 420

gactctacaa catatgcaca ttttctgttc aatgcgtttg atacggacca caatggagct 480

gtgagtttcg aggatttcat caaaggtctt tccattttgc tccgggggac agtacaagaa 540

aaactcaatt gggcatttaa tctgtatgat ataaataaag atggctacat cactaaagag 600

gaaatgcttg atataatgaa agcaatatac gacatgatgg gtaaatgtac atatcctgtc 660

ctcaaagaag atgcacccag acaacacgtc gaaacatttt ttcagaaaat ggacaaaaat 720

aaagatgggg ttgttaccat agatgagttc attgaaagct gccaaaaaga tgaaaacata 780

atgcgctcca tgcagctctt tgaaaatgtg atttaacttg tcaactagat cctgaatcca 840

acagacaaat gtgaactatt ctaccaccct taaagtcgga gctaccactt ttagcataga 900

ttgctcagct tgacactgaa gcatattatg caaacaagct ttgttttaat ataaagcaat 960

ccccaaaaga tttgagtttc tcagttataa atttgcatcc tttccataat gccactgagt 1020

tcatgggatg ttctgactca tttcatactc tgtgaatatt caaaagtaat agaatctggc 1080

atatagtttt attgattcct tagccatggg attattgagg ctttcacata tcagtgattt 1140

taaaatacca gtgtttttg ctactcattt gtatgtattc agtcctagga ttttgaatgg 1200

ttttctaata tactgacatc tgcatttaat ttccagaaat taaattaatt ttcatgtctg 1260

aatgctgtaa ttccatttat atacttttaag taaacaaata agattactac aattaaacac 1320

atagttccag tttctatggc cttcacttcc caccttctat tagaaattaa ttttatctgg 1380

tatttttaaa catttaaaaa tttatcatca gatatcagca tatgcctaat tatgcctaat 1440

gaaacttaat aagcatttaa ttttccatca tacattatag tcaaggccta tatactatat 1500

ataattttgg atttgtttaa tcttacaggc tgttttccat tgtatcatca agtggaagtt 1560

caagacggca tcaaacaaaa caaggatgtt tacagacata tgcaaagggt caggatatct 1620

atcctccagt atatgttaat gcttaataac aagtaatcct aacagcatta aaggccaaat 1680

ctgtcctctt tcccctgact tccttacagc atgtttatat tacaagccat tcagggacaa 1740

agaaaccttg actaccccac tgtctactag gaacaaacaa acagcaagca aaattcactt 1800

tgaaagcacc agtggttcca ttacattgac aactactacc aagattcagt agaaaataag 1860

tgctcaacaa ctaatccaga ttacaatatg atttagtgca tcataaaatt ccaacaattc 1920

agattatttt taatcacctc agccacaact gtaaagttgc cacattacta aagacacaca 1980

catcgtccct gttttgtaga aatatcacaa agaccaagag gctacagaag gaggaaattt 2040

gcaactgtct ttgcaacaat aaatcaggta tctattctgg tgtagagata ggatgttgaa 2100

agctgccctg ctatcaccag tgtagaaatt aagagtagta caatacatgt acactgaaat 2160

ttgccatcgc gtgtttgtgt aaactcaatg tgcacatttt gtatttcaaa aagaaaaaat 2220

aaaagcaaaa taaaatgtta aaaaaaaaaa aaaaaaaaa 2259

<210> 72
<211> 250
<212> PRT
<213> Simian sp.

<400> 72

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Met Asn Val Arg Arg Val Glu Ser Ile Ser Ala Gln Leu Glu Glu Ala
  1               5                  10                  15

Ser Ser Thr Gly Gly Phe Leu Tyr Ala Gln Asn Ser Thr Lys Arg Ser
            20                  25                  30

Ile Lys Glu Arg Leu Met Lys Leu Leu Pro Cys Ser Ala Ala Lys Thr
        35                  40                  45

Ser Ser Pro Ala Ile Gln Asn Ser Val Glu Asp Glu Leu Glu Met Ala
    50                  55                  60

Thr Val Arg His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser
65                  70                  75                  80
```

Lys Phe Thr Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn
85 90 95

Glu Cys Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Glu Ile Tyr
100 105 110

Ser Gln Phe Phe Pro Gln Gly Asp Ser Thr Thr Tyr Ala His Phe Leu
115 120 125

Phe Asn Ala Phe Asp Thr Asp His Asn Gly Ala Val Ser Phe Glu Asp
130 135 140

Phe Ile Lys Gly Leu Ser Ile Leu Leu Arg Gly Thr Val Gln Glu Lys
145 150 155 160

Leu Asn Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile
165 170 175

Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ala Ile Tyr Asp Met Met
180 185 190

Gly Lys Cys Thr Tyr Pro Val Leu Lys Glu Asp Ala Pro Arg Gln His
195 200 205

Val Glu Thr Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Val Val
210 215 220

Thr Ile Asp Glu Phe Ile Glu Ser Cys Gln Lys Asp Glu Asn Ile Met
225 230 235 240

Arg Ser Met Gln Leu Phe Glu Asn Val Ile
245 250

<210> 73
<211> 10
<212> PRT
<213> Simian sp.

<400> 73
Ser Asn Ala Lys Ala Val Glu Thr Asp Val
1 5 10